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Formulation and Evaluation of Controlled Release Polyherbal Tablet for Anti-Diabetic Activity

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ABSTRACT

The present study focuses on the formulation and evaluation of a controlled- release polyherbal tablet for anti-diabetic activity, leveraging the combined benefits of multiple herbal extracts known for their glucose-lowering potential. The HPLC chromatograms for *Gymnema sylvestre, Andrographis paniculata, Syzygyium cumini, Cassia auriculata,* and *Cinnamomum verum* provide a detailed analysis of the individual compounds present in each plant extract. Each chromatogram reveals the presence of characteristic compounds, such as gymnemic acids in *Gymnema sylvestre*, andrographolide in *Andrographis paniculata*, anthocyanins in *Syzygium cumini*, and cinnamaldehyde in *Cinnamomum verum.* FTIR analysis reveals the functional groups present in each plant extract, providing insight into their molecular structures. The preliminary phytochemical analysis reveals a wide variety of bioactive compounds across the plant extracts.

The in-vitro drug release studies of the herbal formulations highlight the release profiles of different plant extracts at various concentrations over a 12-hour period. Formulation F4 consistently demonstrates the highest drug release across all the herbal extracts, indicating its superiority in terms of sustained and efficient drug release. For *Gymnema sylvestre*, the release in F4 reaches 94.27% at 12 hours, while *Andrographis paniculata and Syzygyium cumini* also show high release percentages, 92.47% and 89.98%. The F4 formulation, however, exhibited slightly lower inhibition percentages at corresponding concentrations and a higher IC_{50} value of approximately 105.07 µg/ml. As the concentration increased to 500 µg/ml and above, both samples exhibited marked inhibition (over 80% inhibition for acarbose and 75.88% for F4), indicating that both acarbose and F4 formulation could effectively inhibit the target enzyme at higher doses.

Keywords: Controlled release, polyherbal, anti-diabetic, pre-formulation, *In-vitro*, formulation, blood glucose.

INTRODUCTION

The WHO has recently defined traditional medicine (including herbal drugs) as comprising therapeutic

practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today. Traditional medicine is the synthesis of therapeutic experience of generations of practicing physicians of indigenous system of medicine. [1] The use of herbal medicinal products and supplements has increased tremendously over the past three decades with not less than 80% of people worldwide relying on them for some part of primary healthcare. The pharmacological treatment of disease began long ago with the use of herbs. Methods of folk healing throughout the world commonly used herbs as part of their tradition. Traditional Chinese medicine has been used by Chinese people from ancient times. Although animal and mineral materials have been used, the primary source of remedies is botanical. Many herbal remedies found their way from China into the Japanese systems of traditional healing. Ayurveda is a medical system primarily practiced in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment.[2]

Diabetes mellitus (DM) is a metabolic disorder where in human body does not produce or properly uses insulin, a hormone that is required to convert sugar, starches and other food into energy. Absence or reduced insulin in turn leads to persistent abnormally high blood sugar and glucose in tolerance. It is probably an oldest disease known to man. It is also referred as black- death from the 14th century. Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects. Insulin is secreted when the level of blood glucose rises—as after a meal. When the level of blood glucose falls, secretion of insulin stops, and the liver releases glucose into the blood.[3]

PHFs, or polyherbal formulations, have recently became well-known throughout the world due to their unique advantages not found in allopathic medications. To begin with, PHFs are recognized for their high efficiency across a wide variety of illnesses. The medicinal effect of herbal remedies arises from the presence of diverse phytoconstituents, and this effect is enhanced when compatible herbs are combined in PHFs. There are several advantages to polyherbalism that a single herbal preparation does not have. A smaller dose of the herbal product would be necessary to achieve the intended pharmacological activity. The use of smaller quantity will decrease the possibility of adverse effects. PHFs also having multiple types of molecules against a disease complication, so different molecules cure a disease by different mechanism to provide a complete therapy against a disease condition.[4]

Controlled drug delivery can be defined as delivery of the drug at a predetermined rate and/or to a location according to the needs of the body and disease states for a definite time period. Controlled release drug administration means not only the prolongation of the duration of drug delivery, similar to the objective in sustained release and prolonged release, but the term also implies the predictability and reproducibility of drug release kinetics. Oral controlled release drug delivery system is one that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a pre-determined period throughout the course of GI transit. Polymers are becoming very important in the drug delivery field. To control the drug release rate from the formulation, polymers are being used as the main tool. Polymers can be used as taste masking agents, to enhance stability of drug and to modify drug release characteristics.[5]

In vitro pharmacology methods involve drug discovery and development using a wide variety of time and cost-effective techniques. These methods are used to evaluate pharmacodynamics and pharmacokinetics of drugs, replacing traditional animal experiments. In vitro models include transfected cells, cell cultures derived from organisms, and isolated enzyme preparations. Common in vitro techniques include cell

culture, enzyme assays and molecular biology techniques. For herbal medicinal products consisting of one herbal substance without any excipients, the assay can be included in the specification of the herbal substance, if justified. Finally, in cases of multi-component herbal medicinal products where an assay of each herbal substance is not possible, the applicant must justify how reproducibility of the finished product is guaranteed and tested.[6]

MATERIAL AND METHODS

Collection of Herbal plants

The different parts of the plants selected for the study have shown Antidiabetic activity The plants used *Cassia auriculata* (flower), *Cinnamomum verum* (bark), *Syzygium cumini* (seed), *Andrographis paniculata*(leaves), *Gymnema sylvestre* (leaves) were collected.

The Process of Extraction

The powder of 50g of each plant was drenched in 150ml of 99.9% ethanol in a 500ml round bottomed flask and kept for 72hrs for allowing total extraction at room temperature by the cold maceration process. After that, the soaked it was filtered by Whatman's filter paper no. 41. The filtrate was collected in a porcelain dish and evaporated through a rotary evaporator. The semisolid extract was preserved and dried to remove moisture in a hot air oven.

Development of Polyherbal tablet

Controlled-release polyherbal tablets were prepared by using various herbal extracts and polymers. The polyherbal tablets were prepared by using wet granulation method. All the ingredients were added for each formulation and mixed with isopropyl alcohol; a granulating agent was added slowly and mixed thoroughly. After enough cohesiveness was gotten, the mass was sieved thorough the sieve mesh. The granules were dried at 40^{o}C for 30 min and afterwards passed through the sieve. Magnesium stearate was at last included as glidant and lubricant for each group of granules. The tablets were compressed utilizing a Rotary tablet compression machine.

Evaluation of Polyherbal tablet blends

Bulk density(ρb):

It is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volume measuring apparatus into a cup. It is expressed in g/ml and is given by,

$$\rho b = M/Vo$$

Where, M - is the mass of powder Vo- is the bulk volume of the powder.[7]

Tapped density (ρt):

It is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume change is observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight at a specific distance. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/ml and is given

$$\rho t = M/Vt$$

Where, M - Mass of powder and Vt- Tapped volume of the powder

Angle of repose:

The tangent of angle of repose is equal to the coefficient of friction between the particles. Hence the rougher and more irregular the surface of particles, the greater will be angle of repose. For determination

of angle of repose (θ), the blends were poured through the walls of a funnel which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above a hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\textbf{Tan } \theta = \textbf{h/r,}$$

$$\theta = \textbf{tan-1 (h/r)}$$

Where, θ - angle of repose, h- height in cm and r- radius in cm.[9]

Carr's index:

Carr's index has been used as an in direct method of quantifying powder flow ability from bulk density; this method was developed by Carr. The percentage compressibility of a powder is direct measure of the potential powder arch or bridge strength and stability and is calculated according to following equation.

Carr's index(%compressibility) =100X (1- Db/Dt)

Where Db=bulk density, Dt= tapped density[10]

Standardization of polyherbal tablet

Thickness:

Vernier calliper scale was used for the determination of the thickness of tablets, which gives accurate measurements and provides information of the variation between the tablets. Three tablets from each formula were taken and the average thickness of each formula was obtained.

Uniformity of weight:

The weight variation study was performed by weighing 20 tablets individually and finding the average weight. The deviation of the weight of the tablets from the average weight was determined as the weight variation. Not more than 2 of individual weight of tablets out from the average weight by more than the percentage deviation and none deviate by more than twice the percentage.

Hardness test:

Hardness test is defined as the force which is required to break a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared tablet was determined by using Monsanto hardness tester. It was expressed in kg/cm^2.

Friability test:

Friability of the prepared tablets was determined using Roche Friabilator. Pre-weighed 10no's of tablet was placed in the friability apparatus and subjected to25 rpm in 4 min. tablets were dedusted and reweighed. The optimum range for friability is 0.5% - 1%. This test is additionally checking crushing strength of tablet by this test one can check Capping and Lamination.

% Friability = Initial weight of tablets – Final weight of the tablets× 100 Final weight of the tablets

***In-vitro* Dissolution test:**

10 tablets of each formulation were weighed. Their average was taken and crushed into fine powder. The powder equivalent to 100mg was weighed accurately and transferred into 100ml volumetric flak and the volume was made up to 100ml with suitable buffer. The suitable dilution was made to obtain the concentration of 10 µg/ml of herbal extracts. The resulting solution was analyzed at the wavelength respectively and the percentage drug content was calculated.[11]

COMPATIBILITY STUDY FTIR

Infrared spectroscopy can be used to identify a compound and investigate the mixture's composition. The polyherbal materials were subjected to FTIR studies using the Shimadzu FTIR spectrometer model to investigate the interactions. The IR spectra of the test samples were obtained by the pressed pellet technique using Potassium bromide, and the ratio of the sample is 1: 100.

UV SPECTROSCOPY

Development of UV-VIS Spectrophotometric method for estimation of formulated Herbal Tablet Scanning and determination of maximum wavelength (λmax): In order to ascertain the wavelength of maximum absorption of the extract, different concentrations of the extract (10 µg/ml, 20 µg/ml and 30 µg/ml) in 0.1 N HCl were scanned using spectrophotometer within the wavelength range of 400-200 nm against 0.1 N HCl as blank and the wavelength corresponding to maximum absorbance was noted.

Preparation of standard stock solution:

Accurately weighed 100mg of extract was dissolved in 3ml of methanol in 100ml volumetric flask and volume was made up to the mark with 0.1 N HCl to give a clear solution of 1000 µg/ml concentration.

Preparation of working standard solutions and construction of Calibration Curve:

A series of different concentrations of extract were prepared from working stock solution. 0.1, 0.2, 0.3, 0.4, 0.5, 0.6……1.8, 1.9- and 2.0-ml solutions were pipetted out from the working stock solution and were transferred in to 10 ml volumetric flasks. 10,20,30,40 up to 200 µg/ml solutions were obtained respectively on making up the solution to 10 ml with 0.1 N HCl. The absorbances of all these solutions were measured against a blank at respective λmax using a UV double beam spectrophotometer (UV/Vis-8000, Shimadzu, Japan). A standard plot of absorbance v/s concentration of extract gives the standard calibration curve of the extract. This curve was used to determine in vitro drug release and drug content of herbal tablets.

HPLC CHROMATOGRAM

he HPLC analysis of methanolic extract was carried out with Chromatographic system (YL 9100, Korea) consist of autosampler (YL 9150) with 100 µl fixed loop and an YL9120 UV-Visible detector. The separation was performed on a SGE Protecol PC18GP120 (250mm×4.6 mm, 5µm) column at ambient temperature. The mobile phase consists of methanol to water (70:30 v/v) and the separations were performed by using isocratic mode, elution performed at a flow rate of 1 ml/min. The samples were run for 15min. and detection was done at 254 nm by UV detector. All chromatographic data were recorded and processed using autochro-3000 software.

The HPLC analysis of methanolic extract was carried out with Chromatographic system (YL 9100, Korea) consist of autosampler (YL 9150) with 100 µl fixed loop and an YL9120 UV-Visible detector. The separation was performed on a SGE Protecol PC18GP120 (250mm×4.6 mm, 5µm) column at ambient temperature. The mobile phase consists of methanol to water (70:30 v/v) and the separations were performed by using isocratic mode, elution performed at a flow rate of 1 ml/min. The samples were run for 15min. and detection was done by UV detector. All chromatographic data were recorded and processed using autochro-3000 software.[12]

IN-VITRO ANTI-DIABETIC ACTIVITY

Estimation of alpha-amylase activity

To achieve different concentrations, the stock solution of plant extracts was prepared and diluted with 0.06

M sodium phosphate buffer pH 6.9. The-amylase solution in 0.06 M sodium phosphate buffer pH 6.9 was mixed with the plant extract solution. The best pH for maximal enzyme activity is the one above. After 20 minutes at 37 °C, the solution mixture was incubated at 100 °C for 10 minutes before adding the 1% starch solution with di nitro salicylic acid (DNS) solution. Maltose, a by-product of the enzymatic activity, turned the orange-red 3-amino-5 nitro salicylic acid from the alkaline DNS's pale-yellow hue. Using a UV- micro plate reader, this 3-amino-5-nitrosalicylic was detected at 520nm. The enzyme activity calculated for extract and acarbose was used to compute the percentage of enzyme inhibition. The reaction mixture including starch, amylase and DNS served as the control.[13]

$$Enzyme\ activity = \frac{\mu g\ of\ product\ released}{\text{M. w to Maltose x Incubation time}} X100$$

RESULTS

1.PRELIMINARY PHYTOCHEMICAL ANALYSIS

Phytoconstituents	*Gymnema sylvestre*	*Andrograp his paniculata*	*Syzygium cumini*	*Cinnamomum verum*	*Casssia auriculata*
Flavanoids	+	+	+	+	+
Tannins	+	_	+	_	+
Alkaloids	+	+	+	_	+
Steroids	_	_	+	+	_
Glycosides	+	_	+	_	+
Saponins	+	+	+	_	+
Proteins	+	+	+	+	+
Carbohydrates	+	+	+	+	+
Terpenoids	+	+	+	+	_
Phenolic Compunds	+	+	+	_	+

Table:1. Preliminary Phytochemical analysis

2. DEVELOPMENT OF FORMULATION

S. NO	INGREDIENTS	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
1	*Gymnema sylvestre*	10	-	5	10	-	5	-	10	-	5	15	10
2	*Andrographis paniculata*	10	20	-	5	-	10	10	-	20	-	10	10
3	*Eugenia jambolana*	120	100	105	115	120	105	100	120	100	105	105	120
4	*Cassia auriculata*	90	120	120	110	120	110	120	90	110	120	110	120

5	*Cinnamomum verum*	120	110	120	120	100	120	110	120	120	110	120	100
6	HPMC K100	20	25	30	20	20	25	25	20	20	30	25	20
7	Lactose	30	25	30	20	30	20	25	30	30	30	20	20
8	Mag. Stearate	10	15	10	10	10	15	20	10	10	10	10	20
9	PVP	40	35	30	-	-	-	-	-	-	40	35	30
10	Gelatin	-	-	-	40	50	40	40	50	40	-	-	-
	Total	450	450	450	450	450	450	450	450	450	450	450	450

Table:2 Formulation of controlled release polyherbal tablet

3.PRE-FORMULATION STUDIES

Table:3 Pre-formulation studies

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Angle of Repose	32.4	33.7	32.5	32	32.2	33.6	33	32.5	32.9	32.8	30.9	32.4
2	Bulk density	0.530	0.549	0.530	0.551	0.539	0.544	0.537	0.540	0.544	0.541	0.545	0.542
3	Tapped density	0.669	0.668	0.662	0.667	0.659	0.671	0.660	0.658	0.657	0.654	0.671	0.661
4	Carr's index	16.92	20.46	19.85	18.24	18.86	18.39	18.17	19.20	19.04	20.14	20.08	18.79
5	Hausner's ratio	1.20	1.16	1.23	1.23	1.24	1.20	1.22	1.16	1.20	1.21	1.21	1.22

COMPATIBILITY STUDY

3.1 FTIR

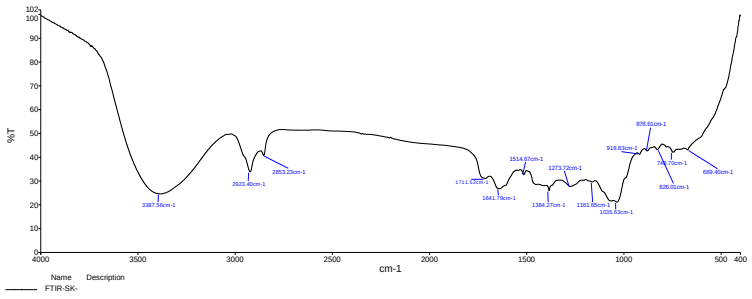

Fig.1. FTIR *Gymnema sylvestre*

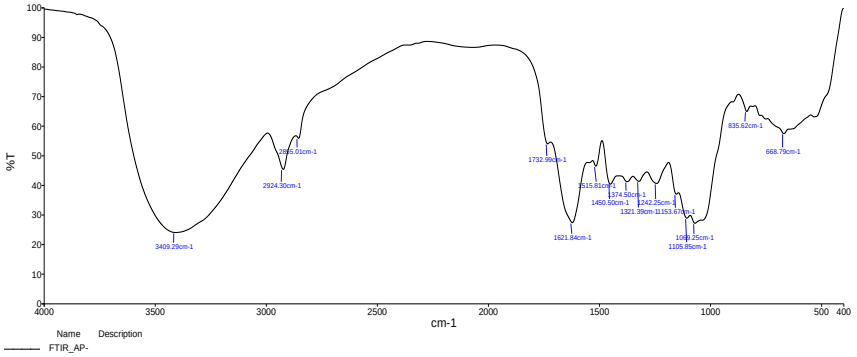

Fig .2 FTIR *Andrographis paniculata*

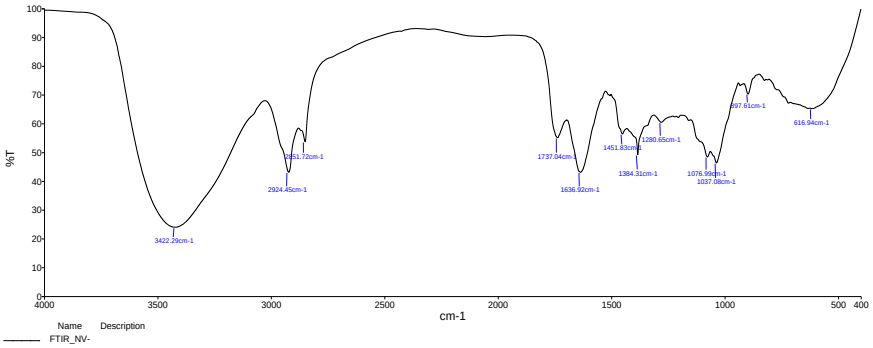

Fig .3 FTIR *Syzygyium cumini*

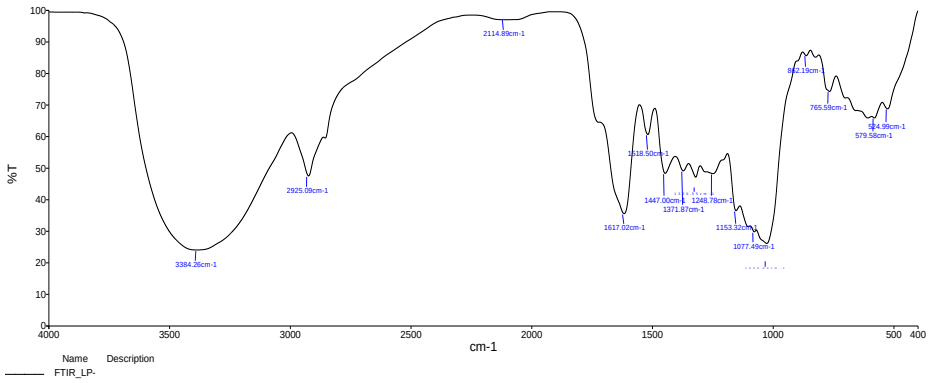

Fig .4 FTIR *Cassia auriculata*

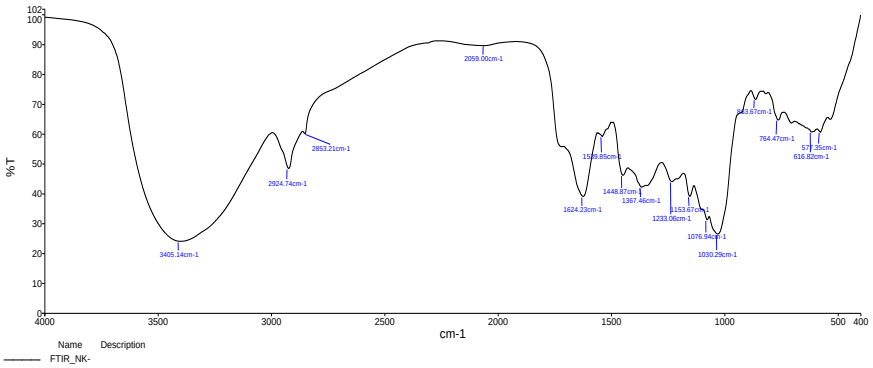

Fig .5 FTIR *Cinnamomum verum*

3.2 STANDARD CALIBRATION CURVE BY UV SPECTROSCOPY

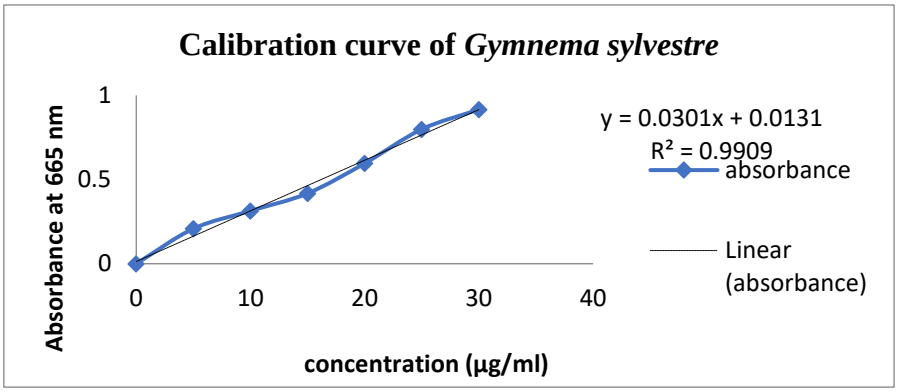

Fig.6 Calibration curve of *Gymnema sylvestre*

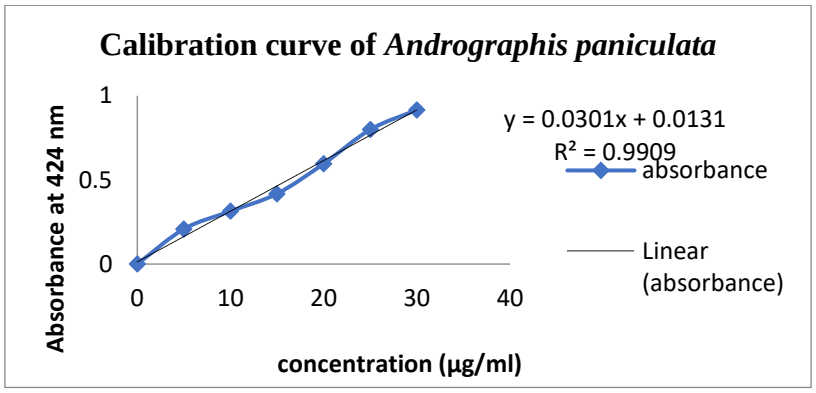

Fig.7. Calibration curve of *Andrographis paniculata*

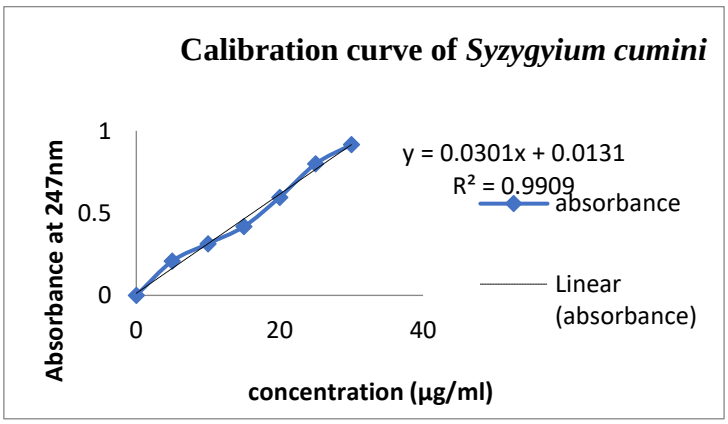

Fig .8. Calibration curve of *Syzygyium cumini*

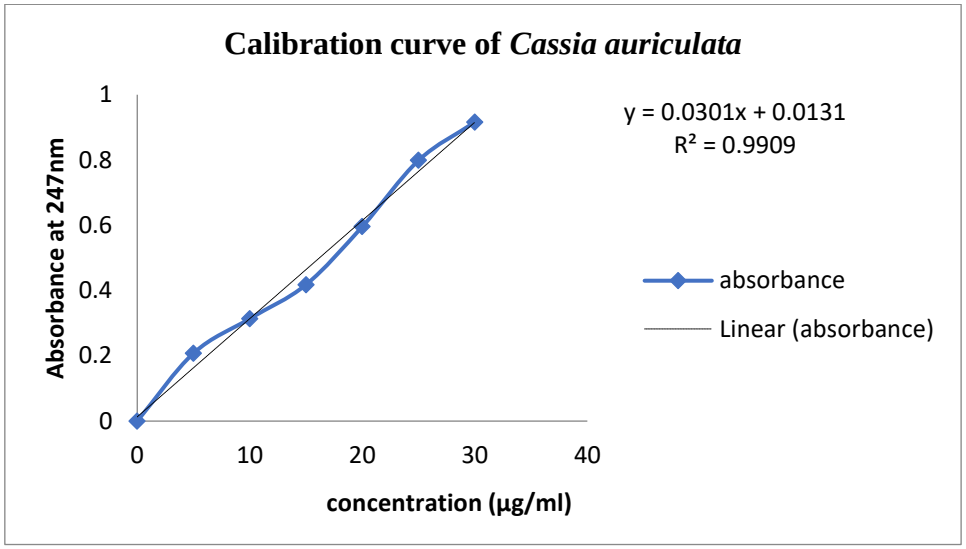

Fig .9. Calibration curve of *Cassia auriculata*

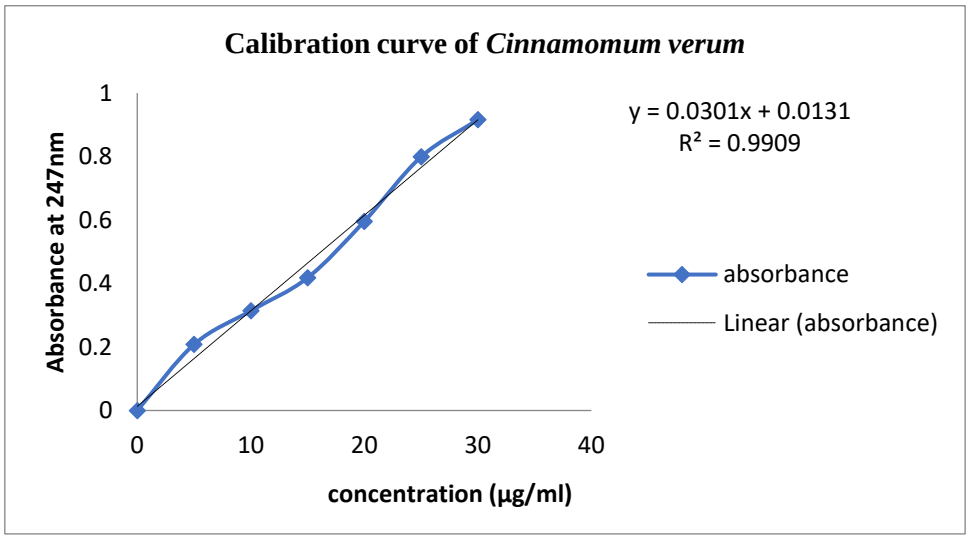

Fig .10. Calibration curve of *Cinnamomum verum*

3.3 HPLC CHROMATOGRAM

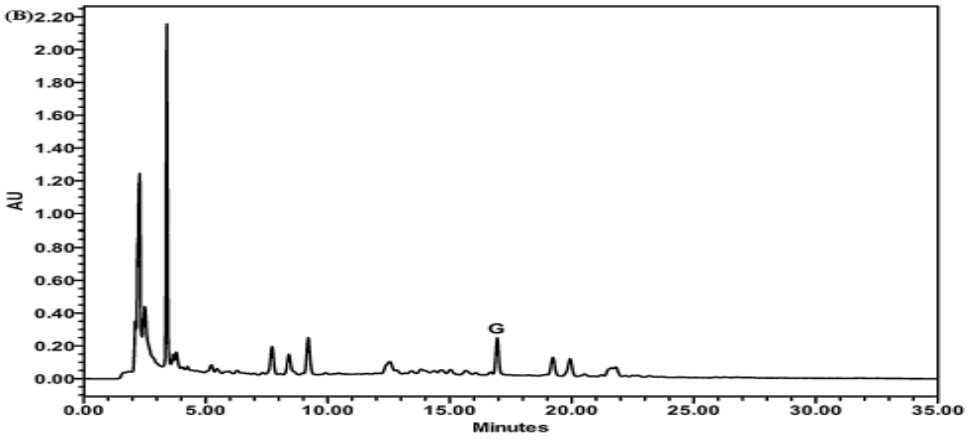

Fig.11. HPLC Chromatogram of *Gymnema sylvestre*

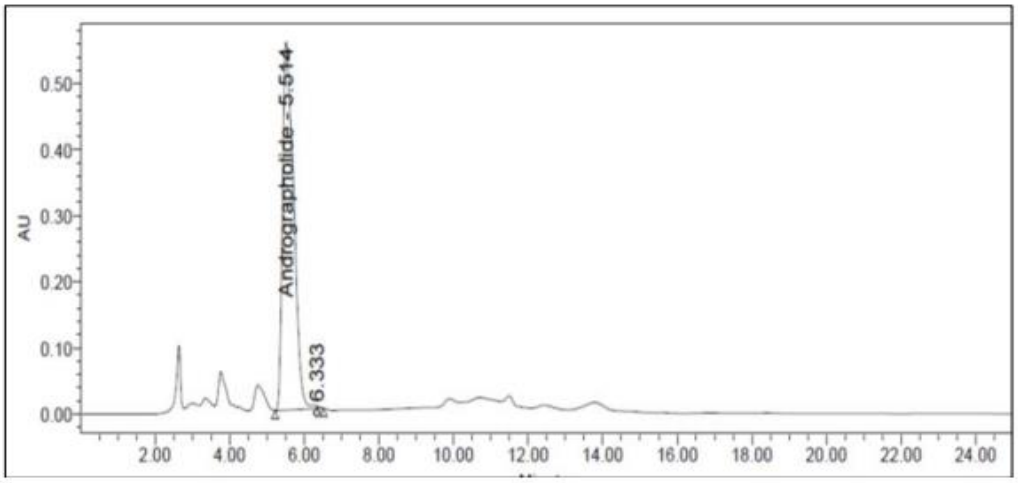

Fig.12. HPLC Chromatogram of *Andrographis paniculata*

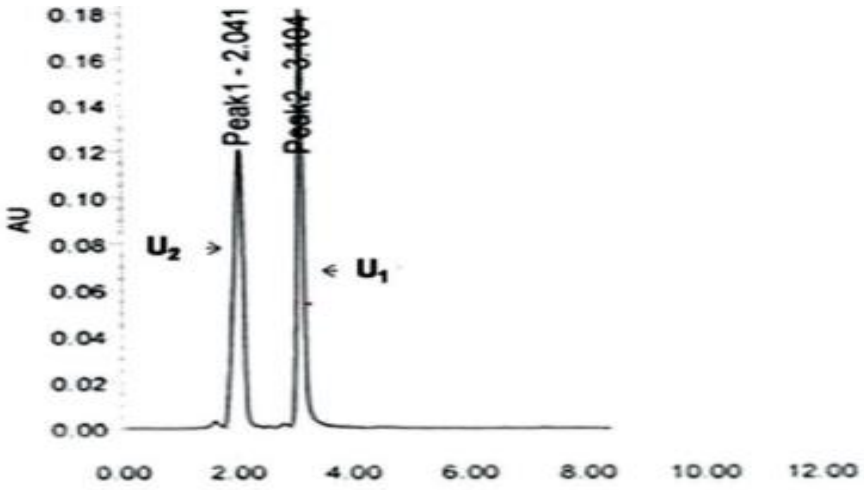

Fig.13. HPLC Chromatogram of *Syzygyium cumini*

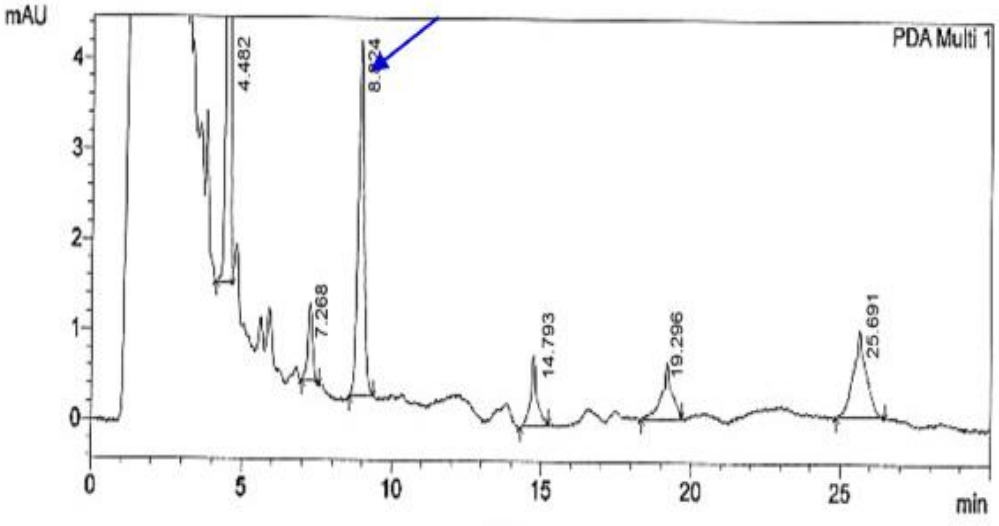

Fig.14. HPLC Chromatogram of *Cassia auriculata*

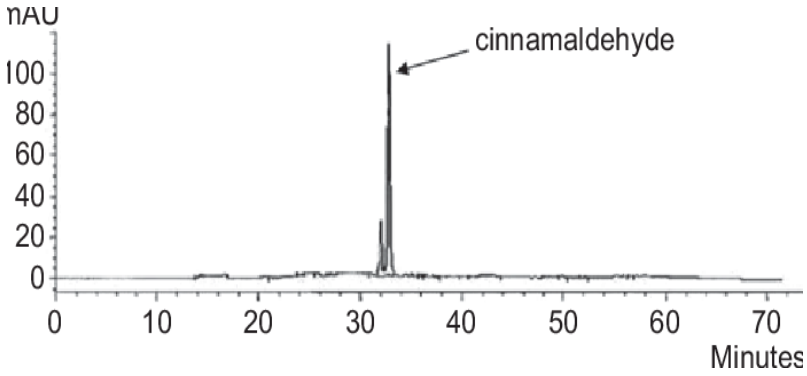

Fig.15. HPLC Chromatogram of *Cinnamomum verum*

3.4 EVALUATION OF POLYHERBAL TABLET

Table:4 Evaluation of Polyherbal tablet

S. NO	INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Uniformity of weight	0.446	0.445	0.445	0.445	0.444	0.443	0.444	0.442	0.446	0.444	0.447	0.443
2	Thickness test	4.65	4.62	4.66	4.65	4.64	4.65	4.63	4.64	4.66	4.62	4.65	4.65
3	Hardness test	6	5.8	6.2	6.06	6.5	6.2	5.76	6.2	6.2	5.8	6.2	6.2
4	Friability test	0.5	0.48	0.48	0.45	0.49	0.47	0.54	0.48	0.49	0.51	0.52	0.52

Fig.16 Polyherbal tablet

BEST FORMULATION: F4

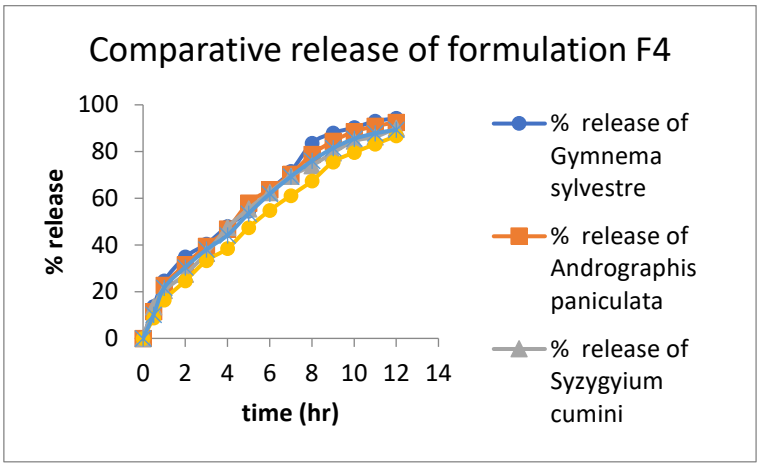

Fig.17 Comparative release profile of Formulation F4

4. PHARMACOLOGICAL STUDIES

***IN-VITRO* ANTIDIABETIC ACTIVITY**

Concentration (µg/ml)	% Inhibition (Acarbose)	% Inhibition of Formulation F4
5	19.6	12.5
10	27.71	17.83
25	39.88	26.95
50	45	33.37
100	57.25	43.93
250	71.79	60.76
500	81.52	75.88
1000	88.89	82.25
IC 50µg/ml	88.92	147.8

Table .5. Percentage Inhibition

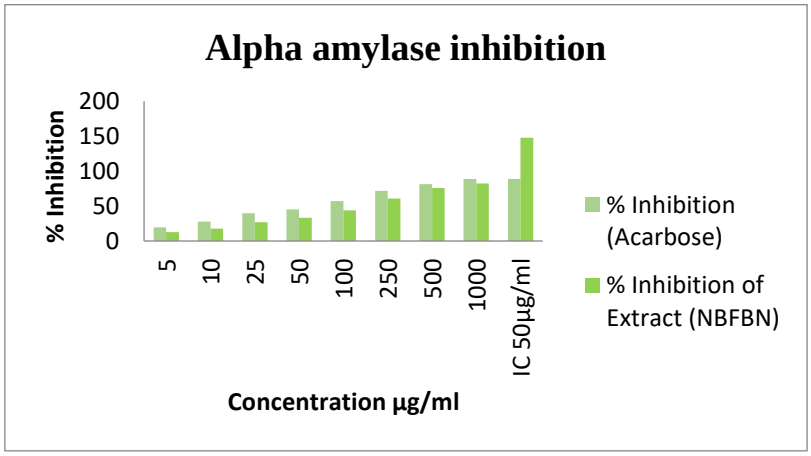

Fig .18 Alpha Amylase inhibition

DISCUSSION

The "Loss on Drying" (LOD) test measures the moisture content in plant materials, which can impact their stability, shelf life, and effectiveness.The ash values of plant materials provide important information about their mineral content and purity. The extractive values provide insight into the solubility of plant compounds in different solvents, which is useful for determining their chemical composition. The preliminary phytochemical analysis reveals a wide variety of bioactive compounds across the plant extracts. *Gymnema sylvestre* and *Andrographis paniculata* both contain a broad range of phytoconstituents, including flavonoids, alkaloids, glycosides, saponins, and proteins, indicating their potential medicinal value. FTIR analysis reveals the functional groups present in each plant extract, providing insight into their molecular structures. *Syzygyium cumini* displays bands for phenolic compounds and flavonoids, confirming its antioxidant properties, and *Cassia auriculata* and *Cinnamomum verum* reveal peaks indicative of saponins, glycosides, and essential oils.

Each chromatogram reveals the presence of characteristic compounds, such as gymnemic acids in *Gymnema sylvestre*, andrographolide in *Andrographi paniculata*, anthocyanins in *Syzygium cumini*, and cinnamaldehyde in *Cinnamomumverum*.The drug content analysis reveals varying levels of herbal extract concentrations across the formulations. **Formulation F4** shows the highest drug content for all plant extracts, with ***Gymnema sylvestre*** at 96.23% and ***Syzygyium cumini*** at 95.17%, indicating a well-balanced and efficient formulation. In contrast, **Formulation F7** exhibits the lowest drug content, especially for ***Cassia auriculata*** (83.66%) and ***Cinnamomum verum*** (76.03%), suggesting potential issues with extraction or formulation consistency. The **in-vitro drug release studies** of the herbal formulations highlight the release profiles of different plant extracts at various concentrations over a 12-hour period. **F4** emerges as the best formulation due to its effective and sustained drug release, making it a promising candidate for further optimization and potential use in antidiabetic therapy. The inhibitory activity of the F4 formulation was evaluated against the standard inhibitor acarbose. From the data, acarbose displayed a dose-dependent inhibition with an IC_{50} value of 88.92 µg/ml, indicating a strong inhibitory effect at relatively low concentrations. The F4 formulation, however, exhibited slightly lower inhibition percentages at corresponding concentrations and a higher IC_{50} value of approximately 105.07 µg/ml. The results also provide valuable insight into optimizing the concentration of F4 formulation for potential therapeuticapplications, where it could serve as an alternative, albeit requiring higher doses compared to acarbose.

CONCLUSION

This study successfully characterized the phytochemical profiles and pharmacological activities of five medicinal plants: Gymnema sylvestre, Andrographis paniculata, Syzygyium cumini, Cassia auriculata, and Cinnamomum verum. The results demonstrated significant variability in phytochemical constituents among the plants, with all exhibiting beneficial compounds such as flavonoids, tannins, and alkaloids, which contribute to their medicinal properties. Formulation F4 consistently demonstrates the highest drug release across all the herbal extracts, indicating its superiority in terms of sustained and efficient drug release. The kinetic analysis of the formulations reveals that all plant extracts follow a Non-Fickian mechanism of drug release, as indicated by the n values ranging from 0.603 to 0.714, suggesting a combination of diffusion and erosion processes particularly Cassia auriculata and Andrographis paniculata, indicate that the release pattern is well fit by this model.

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