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FORMULATION AND INVITRO EVALUATION OF ANTIDIABETIC CAPSULE CONTAINING Madagascar periwinkle, and Gymnema Sylvester

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Abstract:
Preparing capsule formulations using isolated components from *Madagascar periwinkle*, and *Gymnema sylvestre* was the goal of the present work. In order to provide anti-diabetic formulations which have oral hypoglycemic activity which is more effective, with less side effects, and also has higher patient compliance, which provides a variety of benefits. The anti-diabetic activity of *Madagascar periwinkle*, and *Gymnema sylvestre* capsules was investigated.. Angle of repose and bulk density were noted during the preformulation of capsules. Weight variation, pH, moisture content, disintegration speed, in vitro drug release percentage, and in vivo anti-diabetic studies were assessed for finished capsule formulations.

Keywords: Anti-diabetic,Capsule, *Madagascar periwinkle*, and *Gymnema sylvestre.*

INTRODUCTION:

Diabetes mellitus is a metabolic condition characterized by a hybrid of etiology such as chronic hyperglycemia a condition in which protein, lipid, carbohydrate, fats are disrupted which alters the insulin action or secretions. As per the data obtained in 2017 India is known as the "**Diabetes Capital"** of the world [1][2].

Diabetes mellitus is of two types mainly TYPE 1 diabetes mellitus (β-cell destruction which leads to insulin deficiency) only 5-10% public is affected by this. TYPE II diabetes mellitus (range from insulin resistance with relative insulin insufficiency to insulin resistance with largely an insulin secretory abnormality) 90-95% public is affected by type II.[3,4]

The therapeutic efficacy of medicinal plant is well established and they have lack of adverse effect. Due to of lack adverse effect the interest of formulation of antidiabetic medication from natural product has increased in the treatment. Traditional medicine's rational design of newer medications opens up new possibilities in modern healthcare. However, scientific evidence of medicinal plants and phytopharmaceuticals anti-diabetic effectiveness with fewer side effects is still missing. [5]

The medicinal value of *Madagascar periwinkle* is the highest. The *Madagascar periwinkle*, which belongs to the genus *Catharathus*, may be found all over the world, including India. In Hindi, the *Madagascar periwinkle* plant is known as 'Sadabahar', and in Tamil, it is known as 'Nithyakalyani.' It's called 'Nithyakalyani' since it blooms every day of the year, and there are two common types in India. One type has white blooms, while the other has lovely dark pink flowers.Periwinkle is a herb that is used to treat type 2 diabetes. It has been used in traditional medicine for thousands of years to treat a variety of ailments, and it is particularly well-known for its usage in diabetic treatment. These experiments were carried out in order to discover the medicinal advantages of the periwinkle plant in the treatment of diabetes, and they discovered that these plants can help lower blood sugar levels.[6]

The *Gymnema sylvestre*, which belongs to the genus *Gymnema*, may be found all over the world, including India. In Hindi, the *Gymnema sylvestre*plant is known as 'Gudmarr', and in Tamil, it is known as 'Sirukurunkay'. Throughout India, in dry forests up to 600 m, common throughout the district from January to November. Distributed in Asia, Tropical Africa, Malaysia and Srilanka. Leaves powder revealed that G. sylvestre therapy also increased the activities of the enzymes affording the utilisation of glucose by insulin dependent pathways: it controlled phosphorylase levels, gluconeogenic enzymes and sorbitol dehydrogenase. Therefore, the inhibition of the dipeptidyl peptidase activity offers a new therapeutic approach for the management of type 2 diabetes.[7]

MATERIAL AND METHODS:

Gymnema Sylvestre was collected local vendors.*Madagascar Periwinkle*and Neemwere collected from SRMSCET Herbal Garden, Bareilly. Other excipients like Lavender oil, CMC, Magnesium Stearate, Talc were collected from SRMSCET, Bareilly.

Formulation of Antidiabetic Capsule:

The fresh leaves of *Gymnema Sylvestre*(150mg), *Madagascar (*150mg) *Periwinkle*,Neem(30mg) were dried under sunlight for 2-3 days. After drying triturate the leaves in mortar and pestle separately and Pass it through sieve no. 44 for the uniformity of the particle. Mix the powdered leaf together. Then CMC (80mg), Magnesium stearate (50mg), Lavender oil (4drops) and Talc (50mg) was added in the above powdered blend. 10% starch solution was prepared.Mixthe blend and starch paste added uniformly to preparedough and Pass the dough through sieve no. 32 softly to prepare granulesDry the granules in the oven (40-50°C) for the time interval of 5 minute. Now fill the granules in the capsule shell (size-0) with the help of capsule filling machine.

EVALUATION OF FORMULATED TABLET

I. Preformulation studies

a. bulk density
b. Tapped density
c. Angle of repose
d. Compressibility Index (CI)
e. Hausner’s Ratio

a. Bulk Density:

10gm of excipient blend was weighed and pour in a measuring cylinder and allowed to drop on the table from

a height of about 10cm. the volume occupied by the excipient blend was recorded as the bulk volume. The bulk density was calculated by the formula:

Bulk Density(D_b)=Bulk Mass/ Bulk Volume ------1

b. Tapped density

10gm of excipient blend was weighed and pour in a measuring cylinder and tapped volume was obtained by tapping the measuring cylinder fifty times or automatic tapping machine was used until all the void spaces are occupied by powder blend the tapped density was calculated by the help of given formula:

Tapped Density(D_t)=Bulk Mass/ Tapped Volume ------2

A total 3 observations (n=3) were made.

c. Angle of repose

A funnel was kept vertically in a stand at a height above the paper. The bottom of funnel was closed and preweighed 10gm of powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap. The height of heap was measured by using two scales.the angle of repose was calculated by the help of given formula:

$\tan\theta = h/r$----------3

Where, h=height of the heap

R=radius of the heap formed on paper.

d. Compressibility Index (CI):

It is the ability of powder to decrease in volume. Weighed quantity of granules was transferred into 50ml graduated cylinder , volume occupied by granules was noted down. The cylinder was tapped to 500, 700 and 1250taps. The difference between two laps should be less than 2%. The percentage compressibility Index is calculated by using formula:

$CI = D_b - D_t \times 100$----------4

Where, **D_b= Bulk Density**

D_t= Tapped Density

e. **Hausner's Ratio:**

It is the measurement of frictional resisatynce of the granular material. It was determined by the ratio of tapped density and bulk density.

Hausner's Ratio= Vi/Vo----------5

Where, Vi= Tapped density

Vo=Untapped density

Table1: Angle of repose, Compressibility Index (CI) and Hausner's Ratio

Flow property	Angle of repose	Compressibility index	Hausner's ratio
Exacellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

Chemical compatibility studies by FTIR:

IR spectra of drug and polymers and all super disintegrants alone and along with drug in KBr pellets at moderate scanning speed between 4000-400cm-1 was carried out using FTIR. The peak values and the possibility of functional groups shown in spectra were compared with standard values.

Evaluation of Antidiabetic Capsules:
Organoleptic characteristics
Weight variation
Disintegration time
Moisture content
Dissolution time

1. Organoleptic characteristics
The general appearance of a capsule like size, shape, color should be observed.

2. Weight variation
Randomly 20capsules hard gelatin capsules are individually weighed(w1) and the content are removed from the hard gelatin capsule and emptied shells are individually weighed (w2) and net weight is calculated.

Net weight= w1-w2

Percentage weight variation was calculated.

Table 2: Percentage weight variation as per IP

S.No	Dosage Form	Average	%Deviation
1	Hard Gelatin Capsule	<300mg	10%
2	Hard Gelatin Capsule	>300mg	7.5%

3. Disintegration time
One capsule is placed in each of six tubes of disintegration assembly and suspended in water. Disc were added to each tube so that capsule will not floats out of the tube, temperature was maintained at 37°C ±0.5°C for 30minutes.

4. Dissolution time
The Paddle Type Dissolution Apparatus (Electro–Lab 6 basket dissolution apparatus), containing 900 ml of SGF solution was taken into the jar as dissolution medium and temperature was maintained at 37 ºC±2 ºC. The paddle was rotated at 50 rpm for 30 minutes. 5ml of the dissolution medium was withdrawn at predetermined intervals and fresh dissolution medium was replaced. The samples withdrawn were analyzed by U.V. Spectrophotometer (Shimadzu 1800, Kyoto) at 260nm

Invitro release kinetics:
To study kinetics, data obtained from in vitro release were plotted in various kinetic models.

1. Zero order equation:
If the release rate follows zero order then, the slope can be obtained by plotting % drug: releasedVs time in hours. It is an ideal release profile to achieve pharmacological prolonged action. The release rate was independent of concentration.
C=K0t
Where K0 – zero order constant in conc/time
t-time in hours

2. First order equation:

The graph was plotted as log % cumulative drug remaining vs time in hours
log C=log C0-Kt/2.303
where C0- initial concentration of drug
K- first order constant and t-time

3. Higuchi kinetics:

The graph was plotted as % cummulative drug release vs time in hours

Q = Kt1/2

Where K-constant reflecting design variable system

t-time in hours

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow higuchi kinetics of drug release.

4. Hixson and crowell erosion equation:

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and cowell rate equation. The graph was plotted by cube root of % drug remaining Vs time in hours.

Q01/3-Qt1/3=KHCt

Where Qt - amount of drug released in time t

Q0 - initial amount of drug

KHC - rate constant for Hixson crowell equation

5. Korsmeyer – peppas equation:

To evaluate mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time

Mt/M∞= Ktn

Where Mt/M∞ - friction of drug released at time t

t – release time

K – kinetic constant

N – diffusional exponent indicative of the mechanism drug release

The n value could be obtained from slope of the plot of log cumulative % of drug released Vs log time. The results were tabulated.

Table 3: Table showing invitro release kinetics.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n >0.89	Super case-II transport

i. Zero Order Reaction - % Cumulative drug release Vs Time in hrs

ii. First Order Reaction – Log % Cumulative drug remaining Vs Time in hrs

iii. Higuchi kinetics - % Cumulative drug release Vs square root of time

iv. Korsmeyer – Peppas equation- log cumulative % of drug released Vs log time

v. Hixson and Crowell erosion equation – cube root of % drug remaining Vs time in hrs

RESULTS AND DISCUSSION

Formulation of antidiabetic capsule :

The raw materials used in the formulation werecollected from SRMSCET Herbal Garden, Bareilly.

Table 4: Composition of Capsule

S.NO	Excipient	Quantity
1.	Gymnema	150mg
2.	Madagascar Prewinkle	150mg
3.	Neem	30mg

4.	Lavenderoil	4drops
5.	CMC	80mg
6.	MagnesiumStearate	50mg
7.	Talc	50mg

Fig 1: Antiabetic Capsules

Table 5: Herbal drug used in the formulation of Antidiabetic capsule:

Ingredients	Nature	Colour	Odour	Taste
Gymnema	Leaves	Green	Characteristic	Bitter
Madagascarprewinkle	Leaves	Green	Characteristic	Bitter
Neem	Leaves	Green	Characteristic	Bitter
Magnesiumstearate	Coarsepowder	White	Characteristic	Tasteless
Talc	Coarsepowder	White	Characteristic	Tasteless
Lavenderoil	Liquid	Lightyellow	Sweet	characteristic

Table 6:Preformulation

Formulation Batch	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (g/cm^3)	Hausner's Ratio	Angle of Repose
FI	0.500±0.002	0.575±0.014	13.5±0.001	1.13±0.001	25.63±0.690
FII	0.515±0.004	0.580±0.16	14.0±0.029	1.14±0.012	26.20±0.433
FIII	0.505±0.017	0.585±0.12	14.5±0.053	1.15±0.014	25.88±0.111
FIV	0.495±0.034	0.582±0.15	14.4±0.003	1.17±0.040	24.80±0.352
FV	0.505±0.020	0.572±0.20	14.5±0.004	1.14±0.033	25.64±0.428
F VI	0.500±0.017	0.575±0.19	14.1±0.011	1.13±0.042	27.55±0.525

*Mean±SD(n=3)

EVALUATION :

1. Weight variation

The average weight of the formulated capsules indicates that it is under the category of more than 300 mg which means for the capsules to pass this test, a maximum of 18 capsules should not exceed ±10.0%. The percentage deviation should also not exceed a limit of ±20.0% for a maximum of 2 capsules . According to Table 2, not more than 18 capsules exceeded the percentage deviation limit of ±10.0%, and not more than 2 capsules exceeded the limit of ±20.0% which indicates that the capsules passed the uniformity of weight test. This means that each formulated capsule contains the stipulated amount of drug substance and excipients with little variation and this confirms that the encapsulation process was well carried out.

Table 7: Showing results of weight variation of antidiabetic capsule.

Formulation Batch	Average weight (mg)	Percentage Deviation as per IP
FI	**515**	**±10%**
FII	**510**	
FIII	**505**	
FIV	**475**	
FV	**467**	
F VI	**500**	

2. Disintegration time

According to IP the acceptable disintegration time for hard gelatinous capsules should not be more than 30 minutes. Table shows the average time for the disintegration test as 15-25minutes . The results indicated that the capsules disintegrated properly within standard time range, and thus, the drug particles will be amply released for subsequent dissolution

Table 8: Showing results of disintegration time of antidiabetic capsule.

Formulation Batch	Disintegration Time (min)	Standard Limit as per IP
FI	15	**30minutes**
FII	20	
FIII	25	
FIV	15	
FV	18	
F VI	20	

3. Dissolution time

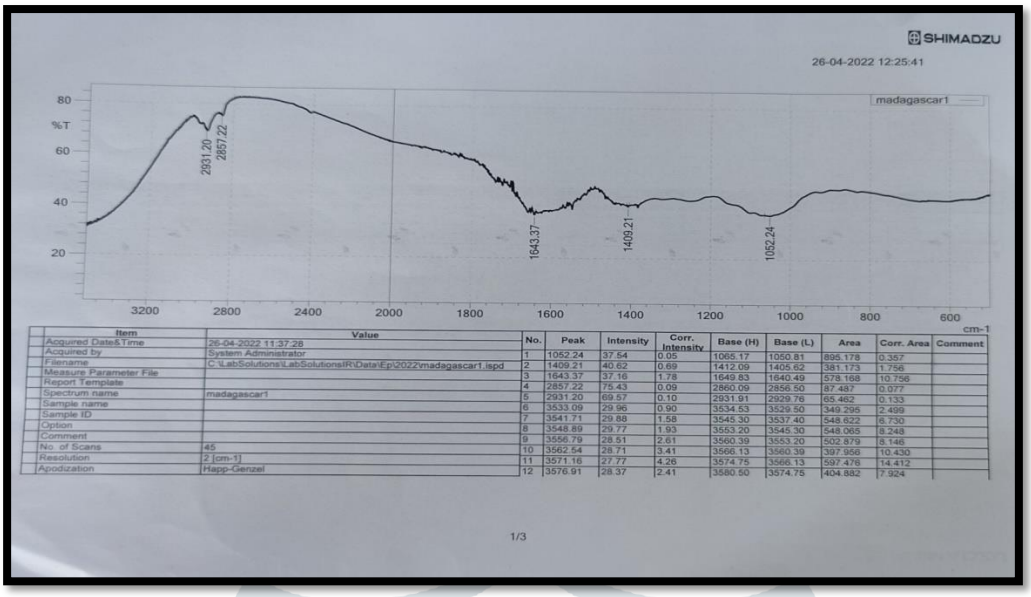
Based on the release profile obtained in Figure , 99.93% of the content had been released at the 50th minute, an indication that the powder passed the dissolution test. This implies that the capsule will be able to release the active ingredients within time for absorption of the active ingredients to occur and ultimately achieve the needed therapeutic effect

Table 9: Showing results of dissolution profile of antidiabetic capsule.

Time	Formulation Batch					
	FI	**FII**	**FIII**	**FIV**	**FV**	**F VI**
10	63.45±0.947	**69.83±0.399**	57.64±0.781	64.52±0.862	52.19±0.685	30.72±0.546
20	79.98±0.572	**83.59±0.805**	74.77±0.526	75.81±0.940	72.93±0.557	51.96±0.385
30	93.27±0.718	**95.32±0.887**	84.57±0.341	89.98±0.557	84.75±0.663	72.43±0.778
40	96.32±0.542	**97.97±0.510**	94.13±0.778	96.75±0.989	93.26±0.560	89.17±0.904
50	98.16±0.622	**99.25±0.715**	98.59±0.722	99.93±0.680	99.14±0.887	98.58±0.933

FTIR:

FT-IR was done to check the interaction present between drug and polymers. IR spectra of drug, polymers and optimized formulation were recorded in the range from 4000- 400 cm-1.



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Sample name	
Sample ID	
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Resolution	2 [cm-1]
Apodization	Happ-Genzel

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	1052.24	37.54	0.05	1065.17	1050.81	895.178	0.357	
2	1409.21	40.62	0.69	1412.09	1405.62	381.173	1.756	
3	1643.37	37.16	1.78	1649.83	1640.49	578.168	10.756	
4	2857.22	75.43	0.09	2860.09	2856.50	87.487	0.077	
5	2931.20	69.57	0.10	2931.91	2929.76	65.462	0.133	
6	3533.09	29.96	0.90	3534.53	3529.50	349.295	2.499	
7	3541.71	29.88	1.58	3545.30	3537.40	548.622	6.730	
8	3548.89	29.77	1.93	3553.20	3545.30	548.065	8.248	
9	3556.79	28.51	2.61	3560.39	3553.20	502.879	8.146	
10	3562.54	28.71	3.41	3566.13	3560.39	397.956	10.430	
11	3571.16	27.77	4.26	3574.75	3566.13	597.476	14.412	
12	3576.91	28.37	2.41	3580.50	3574.75	404.882	7.924	

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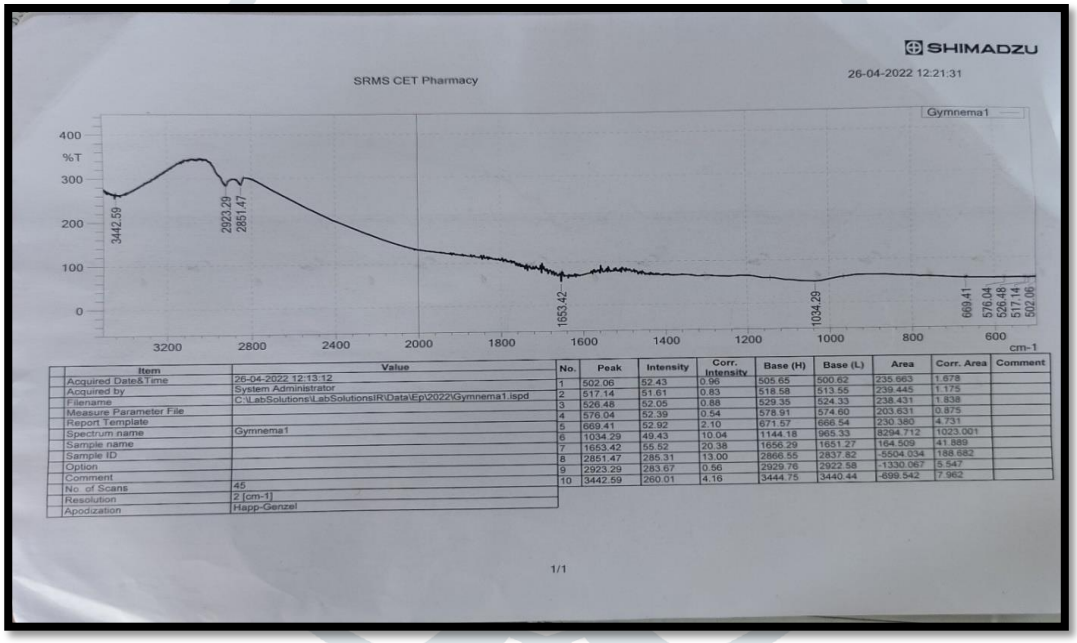
Figure 1: FTIR of Madagascar prewinkle



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Sample name	
Sample ID	
Option	
Comment	
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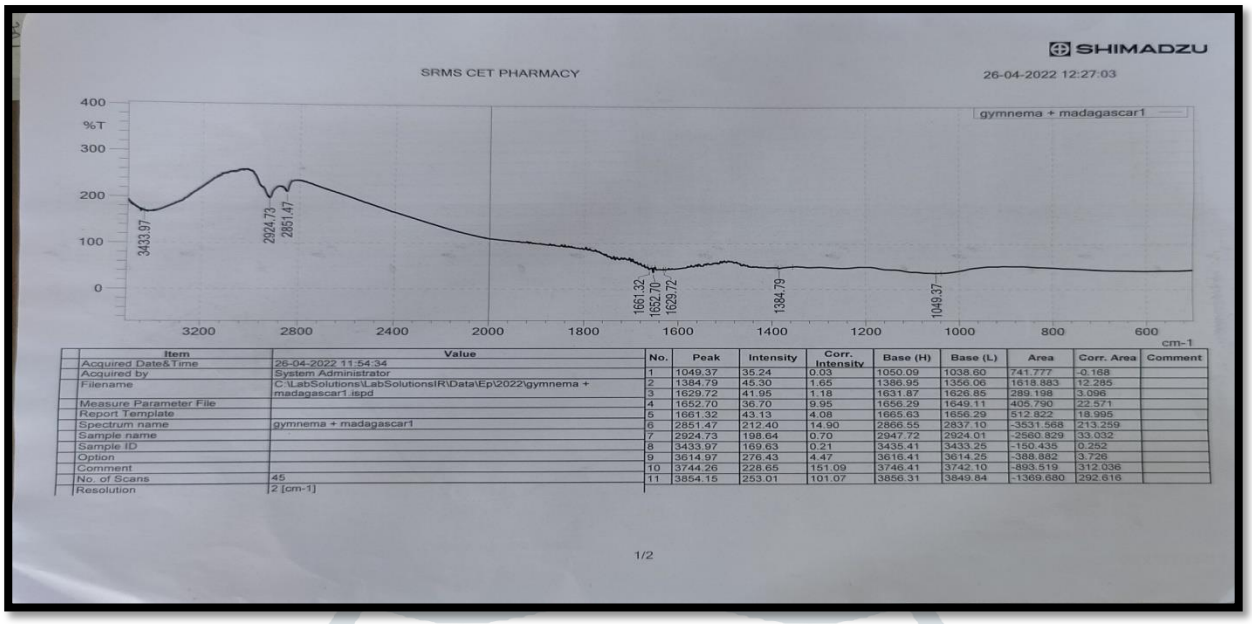
Resolution	2 [cm-1]
Apodization	Happ-Genzel

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	502.06	52.43	0.96	505.65	500.62	235.663	1.678	
2	517.14	51.61	0.83	518.58	513.55	239.445	1.175	
3	526.48	52.05	0.88	529.35	524.33	238.431	1.838	
4	576.04	52.39	0.54	578.91	574.60	203.631	0.875	
5	669.41	52.92	2.10	671.57	666.54	230.380	4.731	
6	1034.29	49.43	10.04	1144.18	965.33	8294.712	1023.001	
7	1653.42	55.52	20.38	1656.29	1651.27	164.509	41.889	
8	2851.47	285.31	13.00	2866.55	2837.82	-5504.034	188.682	
9	2923.29	283.67	0.56	2929.76	2922.58	-1330.067	5.547	
10	3442.59	260.01	4.16	3444.75	3440.44	-699.542	7.962	

1/1

Figure 2: FTIR of Gymnema



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Sample name	
Sample ID	
Option	
Comment	
No. of Scans	45
Resolution	2 [cm-1]

No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area	Comment
1	1049.37	35.24	0.03	1050.09	1038.60	741.777	-0.168	
2	1384.79	45.30	1.65	1386.95	1356.06	1618.883	12.285	
3	1629.72	41.95	1.18	1631.87	1626.85	289.198	3.096	
4	1652.70	36.70	9.95	1656.29	1649.11	405.790	22.571	
5	1661.32	43.13	4.08	1665.63	1656.29	512.822	18.995	
6	2851.47	212.40	14.90	2866.55	2837.10	-3531.568	213.259	
7	2924.73	198.64	0.70	2947.72	2924.01	-2560.829	33.032	
8	3433.97	169.63	0.21	3435.41	3433.25	-150.435	0.252	
9	3614.97	276.43	4.47	3616.41	3614.25	-388.882	3.726	
10	3744.26	228.65	151.09	3746.41	3742.10	-893.519	312.036	
11	3854.15	253.01	101.07	3856.31	3849.84	-1369.680	292.616	

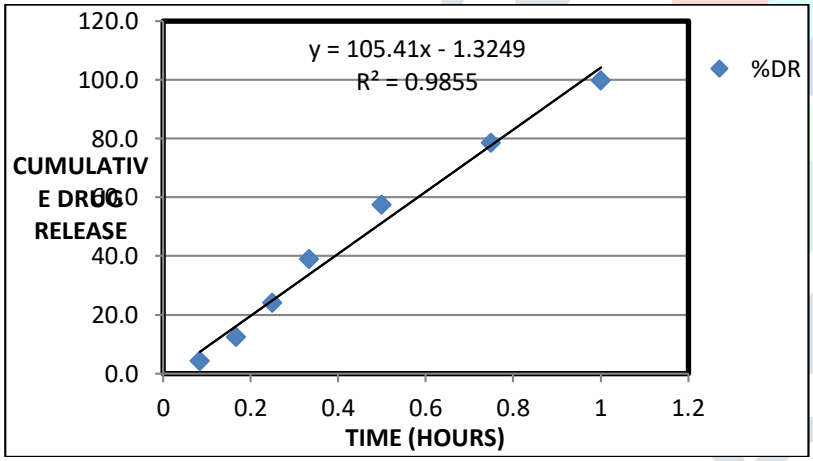
1/2

Figure 3: FTIR of Gymnema + Madagascar periwinkle

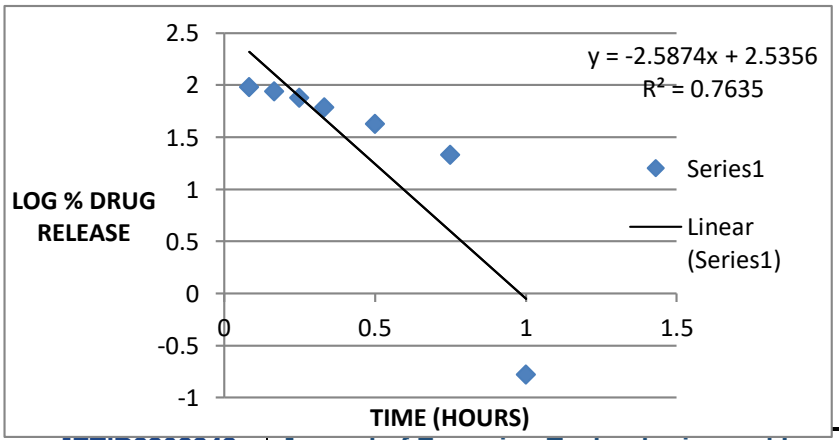
DRUG RELEASE KINETICS

Different models were fit in optimized batch and the graph was plotted for all the models.

ZERO ORDER KINETICS



FIRST ORDER KINETICS



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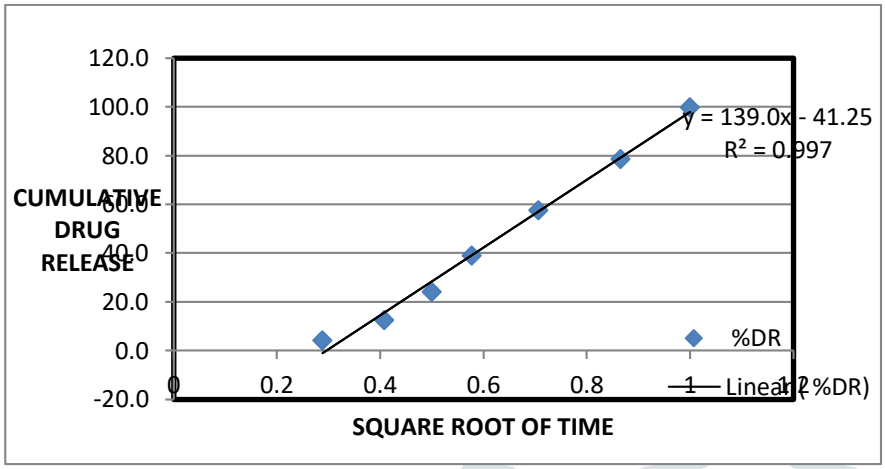
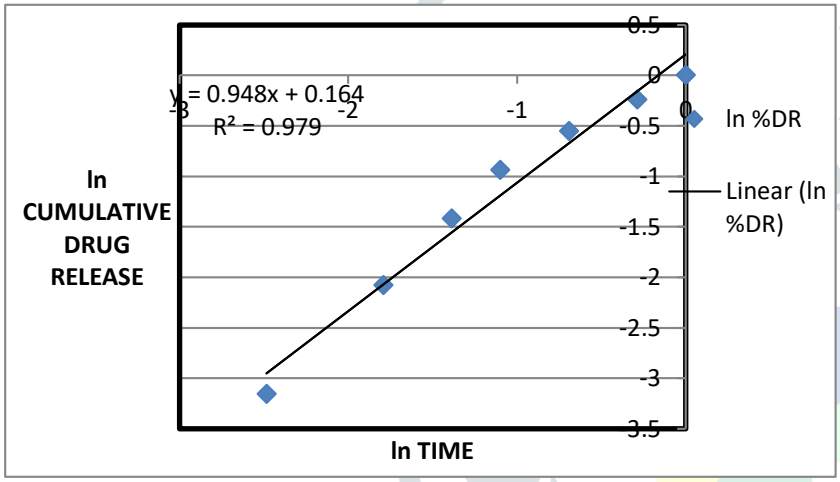


KROSSMEYER PEPPAS



CONCLUSION:

Formulation of Madagascar periwinkle and Gymnema into capsule form using suitable excipients was also found effective as an anti-diabetic drug as compared to the negative control. It is therefore suggested that while Madagascar prewinkle and Gymnema can be formulated into capsules for better compliance and convenience based on this preliminary study, more studies are recommended to understand its possible interactions with excipients and stability problems that the capsules may encounter on storage, pharmacokinetics and potential adverse effects. Madagascar prewinkle and Gymnema has been found to exist in many plants as glycosides with different glycosidic links which have been shown to possess potent anti-diabetic properties together with other biological activities such as anticancer, antimicrobial, anti-inflammatory, antioxidant and anti cholesterolemic properties. In future it can be used as a potential dosage form for anti-diabetic drug.

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