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Research

Formulation And Evaluation Of Solid Lipid Nanoparticles Loaded With Herbal Extracts (Poly Herbal Formulation) Showing Anti-Diabetic Activity Of *Tinospora Cordifolia*

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Abstract

Tinospora Cordifolia-loaded SLNs to improve its efficiency for treatment of diabetes. *Tinospora Cordifolia*-loaded SLNs were prepared by modified high shear homogenization and ultrasonication method using different concentration of solid lipid (Compritol 888 ATO, Cholesterol) and stabilizers (Tween 80 or Span20) The physicochemical properties and the *in vitro* release study for all *Tinospora Cordifolia*-loaded SLNs were investigated. Furthermore, the optimized *Tinospora Cordifolia*loaded-SLN formula. The results showed that *Tinospora Cordifolia*loaded-SLNs were almost spherical shape having colloidal sizes with no aggregation. The drug entrapment efficiency ranged from 89% to near 100%. The zeta potential values lie between -10and -30 mV presenting good stability. From the results F4 considered as optimised formulation. *Tinospora Cordifolia*showed prolonged *in vitro* release from SLNs dispersion. Findings of the study suggest that the developed *Tinospora Cordifolia*loaded SLNs have superior significant fast therapeutic index in treatment of diabetesThe preliminary phytochemical analysis of the *Tinospora Cordifolia* Solid lipid nanoparticles revealed the presence of Alkaloids, Tannins, Anthraquinones, Flavonoids, Saponins, Triterpenes, Sterols, Coumarinas the possible biologically active principles.

Keywords: *Tinospora Cordifolia*, Solid lipid nanoparticles and anti-diabetic activity.

INTRODUCTION

Solid lipid nanoparticle

Recent years it has become more evident that the development of new drugs alone is not sufficient to ensure progress in drug therapy. I*n vitro* obtained are more exciting but very often followed by disappointing results *in vivo*. Main reasons for this therapy failure include:

- Insufficient drug concentration due to poor absorption, rapid metabolism and elimination (e.g., peptides& proteins),
- Drug distribution to other tissues combined with high drug toxicity (e.g., anticancer drugs)**,**
- Poor drug solubility which excludes i.v. injection of aqueous drug solution,
- High fluctuation of variable plasma levels due to unpredictable bioavailability after peroral administration, including the influence of food on plasma levels (e.g., cyclosporine).

To overcome these biopharmaceutical challenges, versatile formulation approaches are required which will accommodate the physicochemical properties of the individual drug while simultaneously exploiting the physiological environment. Solid lipid nanoparticles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs**.**

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of treatment. This idealized objective points to the two aspects most important to drug delivery namely spatial placement and temporal delivery of a drug. Spatial placement relates to targeting of drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. An appropriately designed controlled release drug-delivery system can be a major advance towards solving these two problems. It is for this reason that the science and technology responsible for development of controlled-release pharmaceuticals has been, and continues to be the focus of a great deal of attention in both industrial and academic laboratories.

Conventional drug therapy

To gain appreciation for the value of controlled drug therapy, it is useful to review some fundamental aspects of conventional drug delivery. Consider single dosing of a hypothetical drug that follows a simple one-compartment pharmacokinetic model for disposition. Depending on the route of administration, a conventional dosage form of the drug e.g.: A solution, suspension, capsule tablet etc. can produce a drug blood level versus time profile. The term drug blood levels refer to the concentration of drug in blood or plasma, but the concentration in any tissue could be plotted on the ordinate. Administration of a drug by either intravenous injection or an extra vascular route, e.g., orally, intramuscularly or rectally does not maintain drug blood levels within the therapeutic range for extended periods of time. The short-duration of action is due to the inability of conventional dosage forms to control temporal delivery. If an attempt is made to maintain drug blood levels in the therapeutic range for longer periods by for e.g., increasing the initial dose of an intravenous injection, toxic levels can be produced at early times. This approach obviously is undesirable and unsuitable. An alternative approach is to administer the drug repetitively using a constant dosing interval, as in multiple-dose therapy. In this case the drug blood level reached and the time required to reach that level depend on the dose and the dosing interval. There are several potential problems inherent in multiple dose therapy.

1. If the dosing interval is appropriate for the biological half-life of the drug, large peaks and valleys in the drug blood level may result. For e.g., drugs with short half-lives require frequent designs to maintain constant therapeutic levels.
2. The drug blood level may not be within the therapeutic range at sufficiently early times, an important consideration for certain disease states.
3. Patient non-compliance with the multiple-dosing regimens can result in failure of this approach.

In many instances, potential problems associated with conventional drug therapy can be overcome. When this is the case, drugs given in conventional dosage forms by multiple dosing can produce the desired drug blood level for extended period of time. Frequently, however these problems are significant enough to make drug therapy with conventional dosage forms less desirable than controlled-release drug therapy. This fact, coupled with the intrinsic inability of conventional dosage forms to achieve spatial placement, is a compelling motive for investigation of controlled-release drug delivery systems.

MATERIALS AND METHOD

Butea MonospermaProcured From Local Market Hyderabad, Provided by SURA LABS, Dilsukhnagar, Hyderabad.Compritol 888 ATOProcured from Gattefosse Pvt. Ltd., Mumbai, CholesterolPurchased from Merck

Limited, Mumbai (India), Tween 80 Purchased from SD Fine- Chem Limited, Mumbai, Span 60Purchased from Loba Chemie Pvt Ltd. (Mumbai, India), EthanolPurchased from SD Fine- Chem Limited, Mumbai, Carbopol 934 Purchased from S. D. FineChemicals Ltd. (Mumbai, India), TriethanolaminePurchased from Merck Limited, Mumbai (India), Propylene glycolPurchased from SD Fine- Chem Limited, Mumbai, Alloxan Quali Kems Fine Chem Pvt, Ltd, Vadodara. Methanol ChangshuYangyuan Chemicals, hina .Alcohol Changshu Yangyuan Chemicals, China.Glibenclamide Orchid Pharma Ltd, Chennai.

Plant collection and identification

Tinospora Cordifolia is an aromatic much branched erect herb with 4 angled stems, bearded nodes leaves. It is a common weed of open lands. For the present study fresh plants were collected from locality and brought to laboratory in air tight polythene bags for further processing.

Preparation of leaf extract

For the preparation of leaf extract, fresh leaves were collected in a beaker and washed several times with water to remove the dust and finally with double distilled water. 10 g washed leaves were cut into fine pieces and crushed with the help of mortar and pestle in 100 ml double distilled water. After grinding the aqueous extract was taken in 250 ml beaker and boiled for 10 min at 80 °C temperature. The plant extract was allowed to cool at room temperature and then filtered with whatman filter paper. The filtrate was centrifuged for 20–25 min at 10000 rpm, the supernatant was collected and stored at 4 °C. This filtrate was used as a stabilizing and reducing agents.

Analytical Method Development

Determination of absorption maxima: Absorption maxima are the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure

For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of methanol (1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (5.5 PH). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maximum was obtained at 283 nm with a characteristic peak.

Preparation of calibration curve

It is slightly soluble in water; hence methanol was used for solubilizing the drug. Stock solution (1 mg/mL) of *Tinospora Cordifolia* was prepared in methanol and subsequent working standards (2, 4, 6, 8 and 10 µg/ml) were prepared by dilution with phosphate buffer of pH-6.8. These solutions were used for the estimation *Tinospora Cordifolia* by UV method. The whole procedure was repeated three times and average peak area was calculated. Calibration plot was drawn between concentrations and peak area. Calibration equation and R^2 value are reported.

Preparation of SLN gel

Preparation of *Tinospora Cordifolia*loaded solid lipid nanoparticles

Extract-loaded solid lipid particleswere prepared by hot homogenizing followed by the ultrasonication method. *Tinospora Cordifolia* was dispersed during about 10g of mixed lipid phase (consisted of Compritol 888 ATO and Cholesterol) maintained at around 5ºC above the melting temperature of mixed lipid and dissolved in a mixture of ethanol. Organic solvents were completely removed employing a rotary flash evaporator. An aqueous phase was prepared by dissolving the stabilizers (Tween 80 or Span20) in distilled water (sufficient to supply 30ml) and heating to an equivalent temperature of the oil phase. The hot aqueous phase was added to the oil phase and homogenization was performed (at 2500rpm and 70ºC) employing a mechanical stirrer for 25 minutes. *Tinospora Cordifolia* loaded SLN was finally obtained by allowing the recent nano-emulsion to chill at temperature, and was stored at 4ºCwithin the refrigerator.

Variables for selection of excipients of solid lipid nanoparticles :

- Compritol 888 ATO(mg)
- Cholesterol(mg)

Table 1: Composition of solid lipid nanoparticles formulations (F1 to F9)

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Tinospora Cordifolia (mg)	100	100	100	100	100	100	100	100	100

Compritol 888 ATO (mg)	1	1.5	2	2.5	3	1.5	2	2.5	1.5
Cholesterol(mg)	0.5	0.7	0.5	0.7	0.5	0.7	0.5	0.7	0.5
Tween 80(mL)	0.1	0.5	0.7	0.8	-	-	-	-	1
Span 60 (mL)	-	-	-	-	0.5	1	1.2	0.5	1
Distilled water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Ethanol(ml)	2	2.5	2	2.5	2	2.5	2	2.5	2
Total amount(mg)	100	100	100	100	100	100	100	100	100

RESULT AND DISCUSSION

The present work was designed to developing Floating Microspheres of Repaglinide using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

CALIBRATION PLOT OF *TINOSPORA CORDIFOLIA* IN PHOSPHATE BUFFER OF ph -6.8

A standard graph of *Tinospora Cordifolia* in phosphate buffer of pH-6.8 was plotted using Absorbance and concentration as shown in Table and Fig. Equation for linearity curve and R^2 were calculated as Y=0.082X +0.001 and R^2 =0.999. *Tinospora Cordifolia* showed maximum absorbance in phosphate buffer (pH 6.8) at 283 nm. The solution obeyed Beer-Lambert's law for concentration range of 2 to 10 µg/mL with regression coefficient of 0.999. Standard curve of prepared Tinospora Cordifolia in phosphate buffer pH 6.8 is shown below.

Table 2: Calibration curve of *Tinospora Cordifolia* in phosphate buffer pH 6.8

Concentration(µg/mL)	Absorbance
0	0
2	0.159
4	0.324
6	0.498
8	0.656
10	0.817

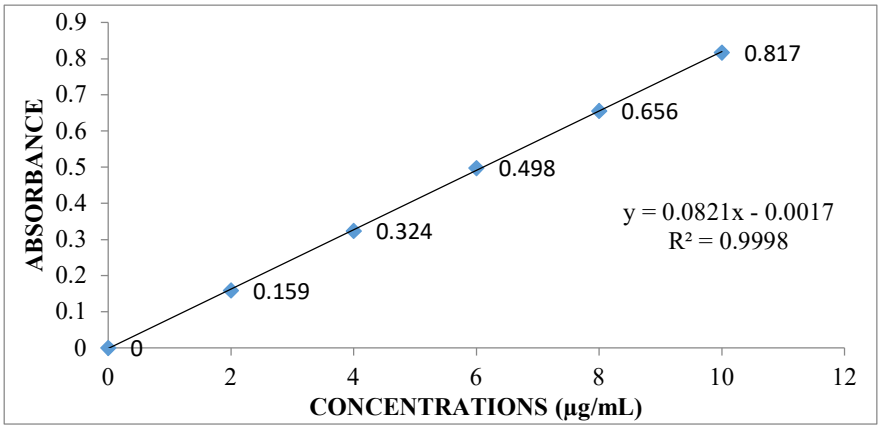

Fig 1: Calibration curve of *Tinospora Cordifolia*

Characterization of solid lipid nanoparticles

Table 3: Percentage yield, Drug Content, Entrapment Efficiency of all solid lipid nanoparticles formulations

FORMULATION	Percentage yield	Drug Content	Entrapment Efficiency
F1	90.36	97.20	95.91
F2	93.51	98.01	97.35
F3	95.28	98.89	97.17
F4	**97.10**	**99.66**	**99.76**

F5	87.35	90.03	98.42
F6	90.51	97.14	97.30
F7	93.62	98.65	92.91
F8	92.02	99.17	96.35
F9	96.96	97.35	90.17

Percentage yield of formulations F1 to F9 by varying drug to lipid ratio was determined and is presented in Table. Highest drug content, Highest Entrapment efficiency observed for F4 formulation.

Table 4: Particle Sizes, PDI, Zeta Potential of all solid lipid nanoparticles formulations

Formulation	Particle Size(nm)	PDI	Zeta Potential(mV)
F1	1165.2	0.668	-26.12
F2	925.8	1.268	-24.81
F3	632.6	1.153	-23.52
F4	**314.3**	**0.168**	**-28.25**
F5	804.1	0.277	-16.55
F6	387.3	0.309	-20.83
F7	329.8	0.698	-22.59
F8	505.4	0.385	-12.11
F9	602.5	0.481	-10.80

The particle size of the all formulations were observed in the range of 314.3 to 1165.2. The less particle size, PDI observed in the F4 formulation i.e., 314.3 nm, 0.168 respectively. The Zeta potential range from -10.80 mV to -28.25 mV to all the formulations. The negative charge on the surface of the nanoparticle is believed to facilitate uptake from the intestine by the Payers patch, leading to the lymphatic circulation, also it is believed to prevent entangling of the nanoparticles in the negatively charged mucous owing to the repulsion of like charges.

Table 5: *In vitro* dissolution studies of F1-F9 SLN formulations in percentage

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	15.21	32.91	28.06	36.84	18.65	32.21	41.34	13.23	25.45
2	30.69	44.83	35.80	50.38	30.76	45.98	46.15	25.67	37.98
4	42.30	52.14	46.96	58.67	36.78	53.12	55.45	32.34	44.82
6	50.93	61.50	53.62	65.26	43.23	60.78	60.12	39.23	50.87
8	55.48	65.41	59.09	70.93	50.25	68.45	68.11	45.89	57.34
10	65.59	73.86	65.18	76.64	55.56	76.78	74.47	51.67	64.87
12	70.15	79.48	68.33	81.14	61.67	80.65	80.78	59.23	68.34
18	77.26	82.08	76.12	86.20	68.98	85.86	88.34	67.56	72.56
24	86.10	90.52	87.86	93.16	82.34	90.22	93.12	80.23	83.67
48	91.43	96.28	96.14	99.34	87.19	95.67	97.01	89.89	86.35

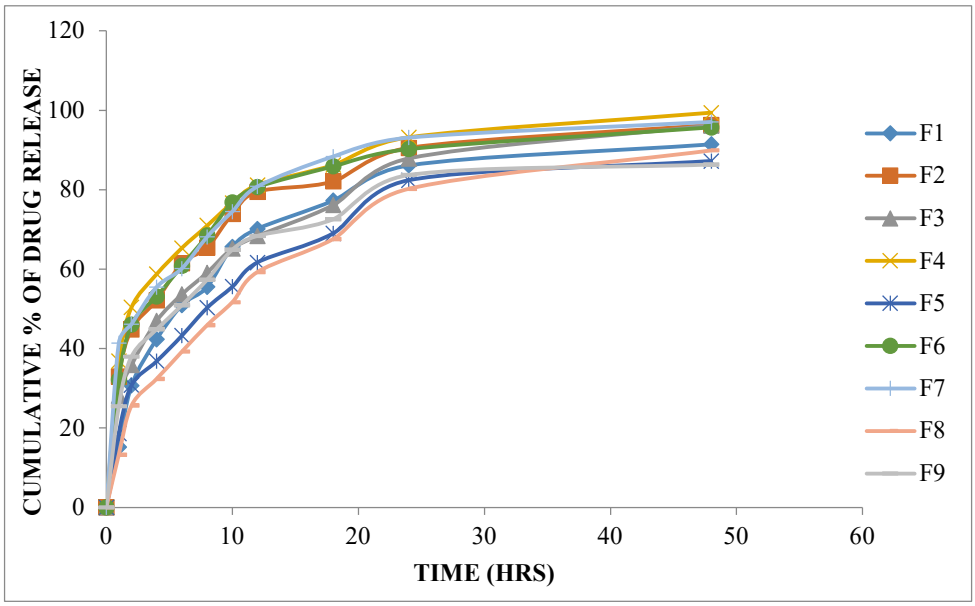

Fig 2: *In vitro* dissolution studies of F1-F9 SLN formulations in percentage

In vitro drug release study of the selected SLNs (F1, F2, F3, F4, F5, F6, F7, F8 and F9) was carried out. The SLNs exhibited 48 hours sustained release pattern. Fifty percent of the incorporated amount of drugs was found to be released during the first 2 hours, followed by a slowed release of 99.34% of the drug up to 48 hours. The *Tinospora Cordifolia* -loaded SLN F4 showed a better release profile of 99.34% by 48 hours. The prolonged release at 48 hours can be attributed to slow diffusion of drug from lipid matrix. The results of *in vitro* drug release are depicted in above Table. F4 formulation was optimised highest drug release (of 99.34% for 48 hours), Hence it was considered as optimised formulation. Based on the dissolution data F4 Formulation was selected for Anti-diabetic activity.

Release Kinetics

`To analyze the drug release mechanism the *in vitro* release was fitted into various release equations and kinetic models first order, zero order, Higuchi and Korsmeyer-peppas. The release kinetics of optimized formulation F4 is shown in Table and in following Figures.

Table 6: Release kinetics of optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
36.84	1	1.000	1.566	0.000	1.800	36.840	0.0271	-0.434	63.16	4.642	3.982	0.659
50.38	2	1.414	1.702	0.301	1.696	25.190	0.0198	-0.298	49.62	4.642	3.675	0.967
58.67	4	2.000	1.768	0.602	1.616	14.668	0.0170	-0.232	41.33	4.642	3.457	1.184
65.26	6	2.449	1.815	0.778	1.541	10.877	0.0153	-0.185	34.74	4.642	3.263	1.379
70.93	8	2.828	1.851	0.903	1.463	8.866	0.0141	-0.149	29.07	4.642	3.075	1.567
76.64	10	3.162	1.884	1.000	1.368	7.664	0.0130	-0.116	23.36	4.642	2.859	1.783
81.14	12	3.464	1.909	1.079	1.276	6.762	0.0123	-0.091	18.86	4.642	2.662	1.980
86.2	18	4.243	1.936	1.255	1.140	4.789	0.0116	-0.064	13.8	4.642	2.399	2.243
93.16	24	4.899	1.969	1.380	0.835	3.882	0.0107	-0.031	6.84	4.642	1.898	2.743

99.34	48	6.928	1.997	1.681	-0.180	2.070	0.0101	-0.003	0.66	4.642	0.871	3.771

FTIR

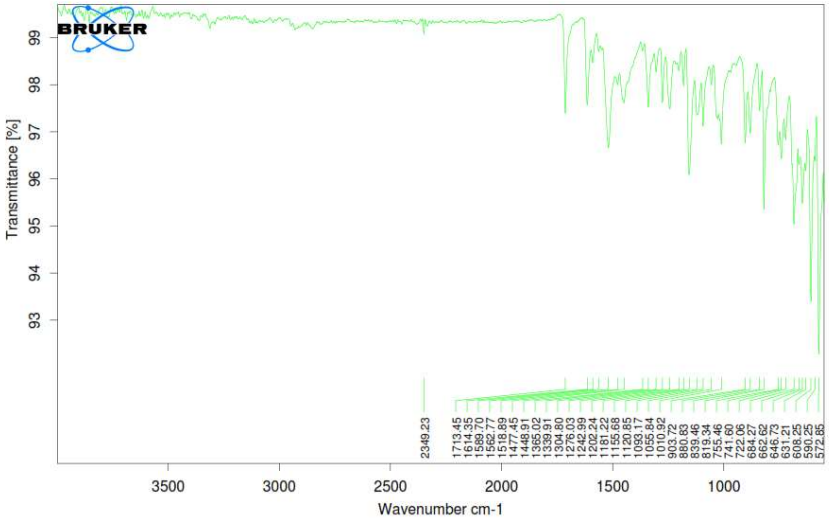

Fig 3: *Tinospora Cordifolia* Pure drug FTIR

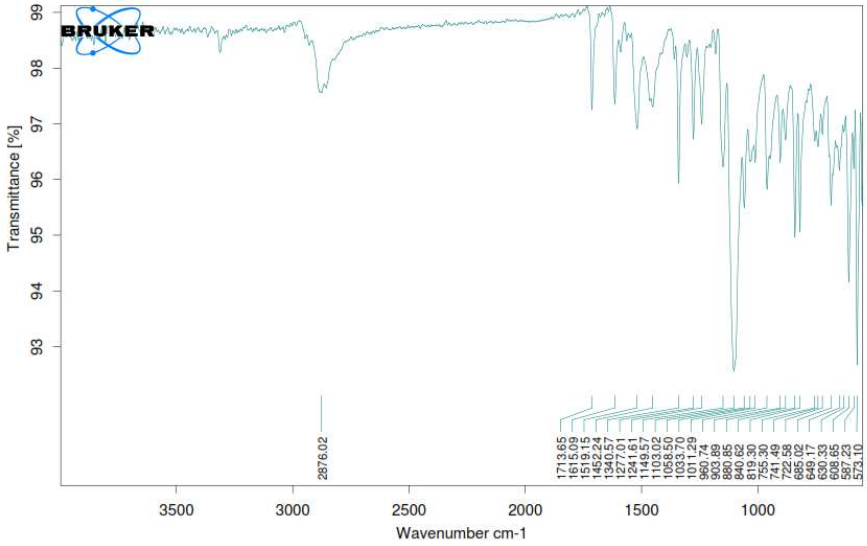

Fig 4: *Tinospora Cordifolia*F4 optimised FTIR

Infrared studies were carried out to confirm the compatibility between the lipid, drug, and selected excipients. From the spectra it was observed that there was no major shifting, as well as, no loss of functional peaks between the spectra ofthe drug and drug-loaded SLN. This indicated no interaction between the drug and other excipients.

SEM

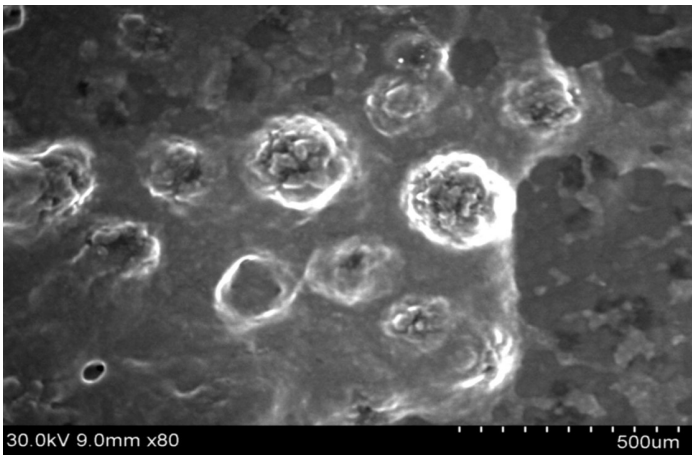

Fig 5: *Tinospora Cordifolia*F4 optimised SLN

SEM studies showed that the *Tinospora Cordifolia*-loaded solid lipid nanoparticleshad a spherical shape with a smooth surface as shown in Figure.

RESULTS AND DISCUSIONS

Phytochemical screening of *Tinospora Cordifolia*

The present investigation concluded that the isolated compounds from the plant *Tinospora Cordifolia*shows the various Pharmacological effects was determined due to the presence of different phytochemical compounds. Further study is needed for the isolation of the constituents present in the plant and its individual pharmacological activity should need to consider and ultimately it should be implemented for the benefit to human beings.

Table 7: Phytochemical screening of *Tinospora Cordifolia*

S.No.	Phytoconstituents	Value
1.	Alkaloids	+
2.	Tannins	-
3.	Anthraquinones	++
4.	Flavonoids	+
5.	Saponins	+
6.	Triterpenes	-
7.	Sterols	-
8	Coumarin	+

Acute toxicity testing

Acute toxicity studies revealed that the *Tinospora Cordifolia*was safe up to 2000 mg/kg of body weight and approximate LD 50 is more than 2000 mg/kg. No lethality or any toxic reactions was observed up to the end of the study period.

Hypoglycemic activity in normal rats

Fasting Blood Glucose Levels (FBGL) were within the range of 90-105 mg/dl in all the groups at 0day. Repeated treatment with the doses of (100 and 200 mg/kg) significantly decrease the blood glucose level on 7^{th}, 14^{th} and 21^{st} day, indicating that the produce significant hypoglycemic activity after repeated administration. Glibenclamide (10mg/kg) also significantly reduced Fasting Blood Glucose Level (FBGL) after repeated administration as compare to normal control group. Changes in FBGL in different groups after repeated dose administration are summarized in Table 8.7.

Repeated administration of nanoparticles had significantly ($p<0.005$) reduced the FBGL on 7^{th}, 15^{th} and 21^{st} day, indicating these extracts can produce hypoglycemia on repeated administration. However hypoglycemic activity was more significant on 7^{th}, 14^{th} and 21^{st} day for Glibenclamide treated as compare with other groups. The results suggest that the possess significant hypoglycemic activity after repeated dose administration.

Effect of *Tinospora Cordifolia* on fasting blood glucose level (FBGL) in normal rats

Table 8: Effect of *Tinospora Cordifolia* on fasting blood glucose level (FBGL) in normal rats

Treatment	Dose (mg/kg)	Blood glucose level(mg/dl)		
		7th day	14th day	21st day
Normal control	-	90.21±1.51	78.10±2.01	73.24±1.10
Glibenclamide	10	83.81±2.31	76.41±0.81	71.30±2.39
TC1	20	78.2±1.06	67.15±3.51	62.52±4.12
TC2	30	89.3±2.61	78.52±0.10	72.21±2.21

Values are expressed as mean± S.E.M. n=6. Significant values were compared with p<0.005, normal control Vs all groups. Parent thesis indicates % reduction in BGL.

Oral glucose tolerance test (OGTT)

The *Tinospora Cordifolia*significantly (P<0.005) suppress the rise in FBGL after glucose load (2g/kg) in rats, at first half-an-hour and up to 2hr time period as compare with other groups Glibenclamide on 8th, 15th and 22nd day. While Nanoparticles produced significant reduction in FBGL. Glibenclamide (10mg/kg) showed (P<0.005) significant suppression in FBGL rise at first half-an-hour, 1hr and normalized FBGL within 2hr.

Table 9:Effect of *Tinospora Cordifolia* on 8th, 15th and 22nd day in normal rats

Treatment	Dose (mg/kg)	Blood glucose level(mg/dl)		
		8th day	15th day	22st day
Normal control	-	91.25±1.26	83.53±2.51	77.13±1.06
Glibenclamide	10	87.06±1.02	77.12±1.81	72.90±1.20
TC1	20	92.19±3.95	83.26±1.80	73.49±1.10
TC2	30	78.11±3.10	67.15±3.52	60.27±3.56

Values are expressed as mean ± S.E.M. n=6. Significant values were compared with P<0.005. Normal control Vs all groups. Paranthesis indicates % reduction in BGL.

Anti-diabetic activity in alloxan induced diabetic rats

Changes in the fasting blood glucose levels in different groups are tabulated in Table No. This data shown that blood glucose level of normal control animals has maintained throughout the study period.

The diabetic control group has shown significant increase in fasting blood glucose levels during this 21st day study period. Glibenclamide (10mg/kg) treated group has shown (p<0.05) significant decrease in fasting blood glucose level during 7th, 14th and 21st day of study period.

Effect of *Tinospora Cordifolia* on antidiabetic activity in alloxan induced diabetic rats

The animals treated with 100 and 200mg/kg of different shown significant decrease (P<0.05) in FBGL on 7th, 14th and 21st day of treatment when compare to other groups of animals. The 30mg have reduced more (%) in FBGL when compared to 20mg except standard group.

Table 10: Effect of *Tinospora Cordifolia* on fasting blood glucose level (FBGL) in Alloxan induced diabetic rats.

Treatment	Dose (mg/kg)	Blood glucose level(mg/dl)		
		7th day	14th day	21st day
Normal control	-	88.12±4.01	77.12±1.92	69.34±1.62
Diabetic control	**10**	299.24±10.50	274.12±24.34	260.21±10.24
Glibenclamide	**10**	265.23±11.30	248.36±71.10	230.21±10.05
TC1	**20**	294.26±12.92	273.10±11.09	220.81±30.35
TC2	**30**	225.13±16.09	186.21±02.12	155.34±55.89

Values are expressed as mean ± S.E.M. n=6. Significant values were compared with P<0.05. Normal control Vs all groups. Paranthesis indicates % reduction in BGL.

Oral glucose tolerance test (OGTT) on 8th, 15th and 22nd day-

The *Tinospora Cordifolia SNP*are significantly (P<0.05) suppress the rise in FBGL after glucose load (2g/kg) in rats, at first half-an-hour and upto 2hr time period as compare with other groups Glibenclamideon 8th,15th and 22nd day. While *Tinospora Cordifolia SNP*produced significant reduction in FBGL. Glibenclamide (10mg/kg) showed (P<0.05) significant suppression in FBGL rise at first half-an-hour, 1hr and normalized FBGL within 2hr.

Table 11: Effect of *Tinospora Cordifolia* on 8th,15th and 22nd day in Diabetic rats.

Treatment	Dose (mg/kg)	Blood glucose level(mg/dl)		
		8th day	15th day	22st day
Normal control	**-**	85.12±2.85	75.28±1.91	63.14±2.89
Diabetic control	**10**	283.25±11.71	251.14±20.95	221.39±19.86
Glibenclamide	**10**	365.89±75.50	286.15±39.52	275.93±15.78
TC1	**20**	264.18±93.56	221.80±96.15	186.55±11.89
TC2	**30**	363.12±10.28	321.18±25.98	282.15±19.12

Values are expressed as mean ± S.E.M. n=6. Significant values were compared with P<0.05. Normal control Vs all groups. Paranthesis indicates % reduction in BGL.

Discussion of anti-diabetic activity

Despite the fact that diabetes has high prevalence, morbidity and mortality globally, it is regarded as non curable but controllable disease. Different synthetic drugs, plant remedies and dietary modification play an effective role in the reduction of the suffering that it causes. The potential role of medicinal plants as antidiabetic agents has been reviewed by several authors. In order to identify the plants with antidiabetic properties various plants have been tested *in-vivo* using animal models, for example rats, against the complications caused by inducers of diabetes, and it has been established that many plants possesses the potential to lower the fasting blood glucose levels and besides help in improving other diabetic complications. The sustained reduction in hyperglycemia automatically decreases the risk of other major complications of diabetes. Effective glucose control is the key for preventing or reversing the diabetic complications and improving the quality of life of the diabetics.

Many natural active compounds have been isolated from plants of different species. These active principles are complex Alkaloids, Tannins, Anthraquinones, Flavonoids, Saponins,Triterpenes, Sterols, Coumarin and others. These compounds have been shown to produce potent hypoglycemic, anti-hyperglycemic and glucose suppressive activities. These effects might be achieved by facilitating insulin release from pancreatic ß-cells, inhibiting glucose absorption in gut, stimulating glycogenesis in liver and/ or increasing glucose utilization by the body.

Crude extracts of *Tinospora Cordifolia nanoparticles*at a dose of 20 and 30mg/kg showed significant effect on the glucose tolerance of rats and it also showed reduction in the fasting blood glucose levels of the normoglycaemic rats, thus revealing the hypoglycemic nature of the extracts. The effect was more pronounced for both extracts. These findings indicate that the extracts might be producing hypoglycaemic effect by a mechanism independent from the insulin secretion e.g. by the inhibition of endogenous glucose production or by the inhibition of intestinal glucose absorption.

Alloxan monohydrate is one of the chemical agents used to induce diabetes mellitus in animals. It induces diabetes by dose dependent destruction of β -cells of islets of langerhans. It is a generator of free radicals of oxygen which cause extensive DNA damage. It was observed that single intravenous dose of alloxan exhibited significant hyperglycemia. Excessive hepatic glycogenolysis and gluconeogenesis associated with decreased utilization of glucose by tissues is the fundamental mechanism underlying hyperglycemia in the diabetic state. As the hyperglycemia induced by alloxan falls under category of mild diabetes and may reverse after a few weeks, the hypoglycemic effect of the plant in hyperglycemic rats was studied during 22 days treatment. The difference observed between the initial and final fasting serum glucose levels of extract treated hyperglycemic rat's revealed ant hyperglycemic effect of leaves of *Tinospora Cordifolia a* throughout the period of study. The effect of the extracts was compared to that of reference standard, Glibenclamide and was found to be significant.

Phytochemical analysis of *Tinospora Cordifolia* revealed the presence of secondary metabolites that have been shown to possess antidiabetic effect in other plants. Flavonoids, alkaloidsandSteroids which were responsible for the antidiabetic effect in other plants were also detected in the extracts of this plant. The presence of phenols in the plant could also be responsible for the antidiabetic effect have been shown to prevent the destruction of β-

cells by inhibiting the peroxidation chain reaction and thus they may provide protection against the development of diabetes. Extracts of *Tinospora Cordifolia* appear to be attractive materials for further studies leading to possible drug development for diabetes. Development of phytomedicine is relatively inexpensive and less time consuming; it is more suited to our economic conditions than allopathic drug development which is more expensive and spread over several years.

SUMMARY

Site-specificand recept or targeting refer to targeting of a drug directly to acertain biological location. In the case of site-specific release, the target is adjacent to or in the disease dorganor tissues, for recept or release, the target are the particular recept or for a drug within an organor tissue. Both of these systems satisfy the spatial aspect of drug delivery and are also considered tobe controlled drug-delivery systems.

Colloiddrug-delivery systems are used to increase the bioavailability of drug substance, to improved rugstability, to sustain and controldrug-release rates, to target drugs to specificsites in the body and to stimulate the immune system. Encapsulation within a colloidal system can protect these therapeutic agents from degradation and deliver them to their sites of action.

Solid lipid nano particles have been reported as an alternative drug delivery device to traditional polymeric nanoparticles. SLNs are in submicron size range (50-1000nm) and are composed of physiologically tolerated lipid components. At room temperature the particles are in solid state. These are made of biocompatible and biodegradable materials capable of incorporating lipophilic and hydrophilic drugs.

The aim of the present study is to make the most benefits of solid lipid nanoparticles as drug delivery system through developing Tinospora Cordifolialoaded Solid lipid nanoparticles (SLNs) Tinospora Cordifolia was elected as drug moleculete formulate Solid lipid nanoparticles and then formulated as trans dermalgels.

The compatibility between pure drug and optimized were detected by FTIR (Bruker Alpha-T) spectra.

Among all the formulation F4 considered as best formulation. Among all the formulations F4 withCompritol 888 ATO(2.5 mg), Cholesterol(0.7 mg)showed the drug release of 99.34% in 48hours and was selected as the ideal formulation.The less particle size, PDI observed in the F4 formulation i.e., 314.3 nm, 0.168*Tinospora Cordifolia* respectively. It had highest zeta potential value hence stable formulation. Among all formulation the data revealed a better fit to the Peppas model with n value less than 0.985 i.e. Fickian diffusion.

The *Tinospora Cordifolia* Solid lipid had hypoglycemic activity because the presence of flavonoids which are rich in treatment of hypoglycemia with less side effects. Flavonoids might be producing hypoglycemic effect by a mechanism independent from insulin secreation e.g. by the inhibition of endogenous glucose production or by the inhibition of intestinal glucose absorption. The present study *Tinospora Cordifolia* Solid lipid nanoparticleswas showed significant effect on glucose tolerance and also showed reduction in fasting blood glucose levels in normal diabetic rats.

The data of the blood glucose level of rats treated with Alloxan (150mg/kg body weight) produced diabetes within 72 hours. After 72 hours of Alloxan administered the blood glucose levels of rats were observed. It was observed that significant lowering of sugar *Tinospora Cordifolia* Solid lipid nanoparticles. The administration of different dose of 20 and 30 mg/kg showed significant anti-hyperglycemic effect at 22^{nd} day which was evident from the 7^{th} day on wards as compared to standard. The extract of *Tinospora Cordifolia* Solid lipid nanoparticles has showed better anti-hyperglycemic effect of the extract on the fasting blood sugar levels on diabetic rats are shown in table. The decreasing blood glucose levels are comparable with that of 10 mg/kg of Glibenclamide. The Glibenclamide (10 mg/kg body weight) shows significant effect on compare to the initial and more significant effect on the 22^{nd} Day compare to the initial. The aqueous and alcoholic extracts of 20 and 30mg/kg body weight shows significant ($P^*<0.05$), effect.

Results of anti-diabetic activity in normal and alloxan induced rats the extracts established the scientific basis for the utility of these plants in the treatment of diabetes. The extracted Solid lipid nanoparticles have shown significant reduction in blood glucose levels in normal and alloxan induced diabetic rats and produced maximum anti-diabetic activity and are higher than the hypoglycemic activity of Glibenclamide in the diabetic rats. In glucose loaded animals, the drug has reduced the blood glucose to the normal levels. It is possible that the drug may be acting by potentiating the pancreatic secretion or increasing the glucose uptake. In conclusion, these Tinospora Cordifolia Solid lipid nanoparticlesshowed significant anti-diabetic effect in normal and diabetic rats after administration. Thus the claim made by the traditional Indian systems of medicine regarding the use of these plants in the treatment of diabetes stands confirms.

CONCLUSION

The study was performed to find out the beneficial effects of *Tinospora Cordifolia* Solid lipid of leaves of *Tinospora Cordifolia*in normoglycaemic rats and alloxan induced diabetic rats and the results reveal that the plant has beneficial effects on blood glucose levels. In current scenario, herbs are the potent sources of medicines

used in the treatment of various disease and disorders. Since, plants are used as medicine there is prompt need of evaluation of plant species, therefore, the present work was conceived to evaluate the phytochemical and pharmacological screening of leaves of Butea Monosperma. Alkaloids,Tannins, Anthraquinones, Flavonoids, Saponins, Triterpenes, Sterols and Coumarin.

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