Original Article

Formulation of Alkaloid Loaded Phytosomes from *Tinospora cordifolia* and *ex-vivo* Intestinal Permeability Study

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ABSTRACT

Background: Phytosomes are newly introduced novel dosage form for improving the bioavailability and therapeutic effect of the herbal drug. The present study aimed to prepare and evaluate the alkaloid loaded phytosome from *Tinospora cordifolia*. **Materials and Methods:** Extracts were screened for total content of phenols, flavonoids and alkaloids. The prepared extract was further used for fractionation and dichloromethane fraction (F3) was used to prepare phytosomes. Phytosome was prepared by using thin film hydration method with different ratio of soya lecithin and cholesterol. The evaluation of phytosome was done by particle size and shape, polydispersity index, differential scanning calorimetry and fourier transfer infrared spectroscopy. Further, *ex-vivo* intestinal permeability study was performed for crude fraction and prepared phytosome to assess the intestinal permeability enhancement. **Results:** The all standardization parameters showed the results within the standard limits, thus confirming the quality and purity of raw material. The particle size and polydispersity index was found within the acceptable limits. The Differential scanning calorimetry and Fourier transfer infrared spectroscopy studies confirmed that there was no drug interaction with the excipients. The *ex-vivo* l permeable analysis of the intestines study was found that the phytosome shows enhancement in intestinal permeability than the crude alkaloid fraction. **Conclusion:** The above results indicated that the prepared alkaloid loaded phytosome shows promising potential in enhancement of intestinal permeability of *Tinospora cordifolia*.

Key words: Phytosomes, *Tinospora cordifolia*, Permeability, Soya lecithin, Cholesterol.

INTRODUCTION

In today's world herbal medicines are becoming increasingly popular for their ability to treat a variety of diseases with less harmful effects and better therapeutic value. A new approach to the production of pharmaceutical products which addresses the constraint of the conventional drug delivery system.[1] Most of the active ingredient in the herbal medicinal products are mainly hydrophilic. Molecules have a minimal effectiveness and are poorly absorbed when taken internally and when used topically. Apart from that due to its bigger molecular size which can't be absorbed via passive diffusion and due to their low lipid solubility limiting its capability to pass throughout the lipid-rich outer membranes of the enterocytes (the cells that line the small intestine) ensuing bad bioavailability of drugs. Therefore, a larger dose is required for dosage administration.[2] To overcome these problems the novel drug delivery system helps to improve the efficacy and reduces the adverse effects of herbal compounds and herbs.[1] Phytosomes are newly introduced novel dosage form for improving the bioavailability and therapeutic effect of the herbal drug.[1] Phytosomes is a nano vesicular drug delivery system in which lipid surrounds and phosphatidylcholine of the lipid bounds to the phytoconstituents of herb extracts. It helps to improve the

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absorption and bioavailability via the pharmacodynamic and pharmacokinetic parameters of herbal extracts.[3]

Tinospora cordifolia (Wild.) Miers, (Guduchi) is a perennial evergreen climber which belongs to the family *Menispermaceae*. In Ayurveda, it is a plant of considerable medicinal value in the indigenous medicinal system and called *Rasayana*. *Tinospora cordifolia* is broadly used folk and traditional Ayurvedic medicine for its, anti-inflammatory, antioxidant, anti-diabetic, anti-arthritic and a variety of different medicinal properties. In the treatment of diabetes it is used as highly potent Ayurvedic drug.[4]

The alkaloids from *T. cordifolia* show poor bioavailability, a high absorption rate and high elimination rate. Hence there is need to design, improve and evaluate an high quality pharmaceutical formulation to enhance its therapeutic effect.[5,6] So the purpose of this study is to prepare and evaluate the phytosomes from alkaloidal fraction of *Tinospora cordifolia* to improve its permeability.

MATERIALS AND METHODS

Materials

Fresh stem of *Tinospora cordifolia* was collected from local region of Vengurla, Dist– Sindhudurga, Maharashtra and authenticated by Dr. HarshaHegade, Scientist E, ICMR, Belagavi, Karnataka. Soya lecithin 30% was purchased from Molychem, Mumbai, India. Cholesterol, BCG reagent, FC Phenol reagent was bought from Himedia laboratories, Mumbai, India. Atropine, Quercetin and Gallic acid was obtained from Sigma Aldrich Chemicals. Ethanol, methanol and dichloromethane was bought from Fisher Scientific, Mumbai.

Methods

The stem of *Tinospora cordifolia* was cleaned with tap water and dried under shade. Then dried stem of *Tinospora cordifolia* was coarsely powdered and kept in the airtight neatly labelled jar till the further use.

Pharmacognostic Studies

Microscopic Study[7,8]

Powder microscopy was done by using Trinocular microscope. For powder microscopy dried stem powder was used.

Physicochemical Studies[8,9]

Physicochemical parameters were calculated according to WHO guidelines.

Extraction of Plant material

Dried stem powder was subjected to cold maceration with 70% v/v ethanol with occasional shaking. Extract was filtered and filtrate was collected in clean glass container. The marc was further expose to soxhlation with ethanol of 95% at 40°C. Filtering of both maceration and soxhelation was combined and optimized at 40°C under reduced pressure using a rotary evaporator (IKA RV 10). Obtained extract was dried and stored in air tight container.[10]

Preliminary Phytochemical screening[9]

The extract of herbal drugs was subjected to phytochemical tests to assess the qualitative chemical composition of the extract by standard method. A phytochemical test was carried out to identify the chemical constituents present in *Tinospora cordifolia* stem extract.

Determination of Total Alkaloid Content

Total Alkaloid Content[11] of *T. cordifolia* stem extract was determined by spectrophotometric method. This method is based on the reaction between alkaloid and bromocresol green (BCG). 1mg of stem extract was dissolved in 2N HCl and filtered. From the above solution 1ml of solution was transferred in separating funnel and then 5ml of BCG solution and 5ml of phosphate buffer (pH 7.4) were added in it. Shake the mixture and formed complex extracted with 1,2,3 and 4ml chloroform respectively with vigrous shaking. Then extract was collected in 10ml volumetric flask and make up the volume with chloroform. Absorbance was measured at 470nm against the same mixture but without stem extract as a blank.

A set of standard atropine reference solution (20, 40, 60, 80 and 100 mcg/ml) was prepared in same manner as above. The calibration curve is depicted in Figure 1. The total alkaloid content of the extract was expressed as mg of AE/g.

Determination of Phenolic Total Content

Total Phenolic Content[11,12] of *T. cordifolia* stem extract was determined by Folin-Ciocalteu colorimetric assay.1ml of stem extract and 9ml of dist. water was taken in 25ml volumetric flask. Add 1ml FC Phenol reagent and shake well. Then, After 5 min, add 10ml of 7% Na_2CO_3 and make upto 25ml with dist. water and incubated for 1hr at room temperature. Absorbance was measured at 765 nm against the same mixture but without stem extract as a blank. A set of standard Gallic acid reference solution

(20, 40, 60, 80 and 100 mcg/ml) was prepared in same manner as above. Calibration curve for standard gallic acid is depicted in Figure 2. The total phenolic content of the extract was expressed as mg of GAE/g.

Determination of Total Flavonoid Content

Total flavonoid content[11,12] of *T. cordifolia* stem extract was determined by aluminium chloride colorimetric assay. 1 ml stem extract and 4 ml dist. water was taken in 10 ml volumetric flask. Added 0.30 ml of 5% sodium nitrate in the above volumetric flask and incubated for 5min at room temperature. After incubation add 0.3 ml of 10% aluminium chloride and again incubated for 5min at room temperature. Then add 2 ml of 1M sodium hydroxide and diluted upto 10ml with distilled water and incubated for 15 min at room temperature. The absorbance was measured at 510nm against the same mixture but without stem extract as a blank.

A set of standard Quercetin reference solution (20, 40, 60, 80 and 100 mcg/ml) was prepared in same manner as above. Calibration curve for standard quercetin is depicted in Figure 3. The total flavonoid content of the extract was expressed as mg of QE/g.

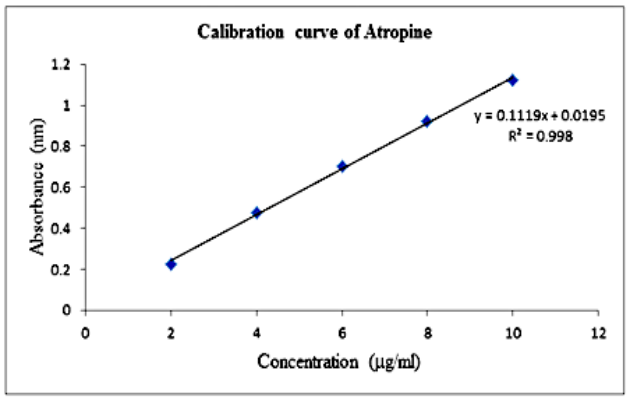

Figure 1: Calibration curve for standard atropine for determination of Total alkaloid content.

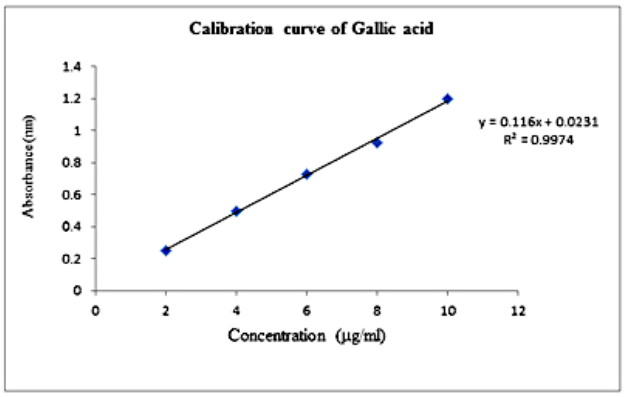

Figure 2: Calibration curve for standard gallic acid for Determination of Total phenolic content.

Fractionation of *Tinospora cordifolia* Stem Extract

Fractionation of *Tinospora cordifolia* stem extract was carried out as per Cos *et al.* method.[13] The stem extract was dispersed in 5% w/v citric acid and washed with dichloromethane. Dichloromethane and aqueous layer were separated. Separated dichloromethane layer was partitioned with 90% v/v methanol and petroleum ether (1:1) to get fraction 1 and fraction 2. Aqueous layer was concentrated to half and pH adjusted to 9.0 with 10% ammonium hydroxide. Aqueous layer was washed with dichloromethane, which gives fraction 3 and fraction 4. Fraction containing alkaloids was used for further studies.

Preparation of Phytosomes

Phytosomes was prepared[14,15] by using thin layer hydration method with different molar ratio of drug, 30% Soya lecithin and cholesterol. Accurately weighed amount of soya lecithin and cholesterol was dissolved in dichloromethane, while drug was dissolved in methanol. The above mixture was taken in round bottom flask and evaporated in rotary evaporator at 40°C at 180 r/min and vacuumed until evaporate the all solvent and thin layer was obtained to RBF. The flask was stored in refrigerator upto 24 hrs. The film was hydrated with mixture of ethanol and water (1:1) in rotary evaporator at 40°C for 1 hr. Once the phytosomal suspension was formed the sonication was done for 30min to reduce the particle size. Total four phytosomal formulations (Table 4) of alkaloid content from *Tinospora cordifolia* were prepared using soya lecithin and cholesterol.

Evaluation of Phytosomes[16-18]

a) Determination of particle size

Vesicles particle size and polydispersity index (PDI) analysis was performed using Nanotrac instrument. 1 ml phytosome suspension was diluted upto 10 ml with

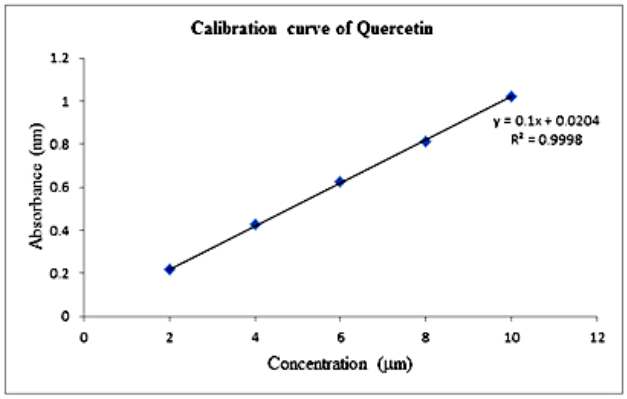

Figure 3: Calibration curve for standard quercetin for determination of Total flavonoid content.

Millipore water and particle size was determined. Particle size and polydispersity index of of the phytosome formulation FS4 is depicted in Figure 4.

b) Vesicles Morphology

Shape and Surface morphology of phytosomes were studied using Trinocular microscopy and scanning electron microscopy (SEM) (Figure 5).

c) Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) analysis was performed on a DSC60 detector. Approximately 2mg of pure alkaloid fraction, physical mixture of fraction with excipients and phytosomes was weighed in an aluminium pan and sealed hermetically. DSC scan was recordedfrom 30°C to 300°C at a heating rate of 10°C/ min under a nitrogen purge. Empty pan was considered as reference (Figure 6).

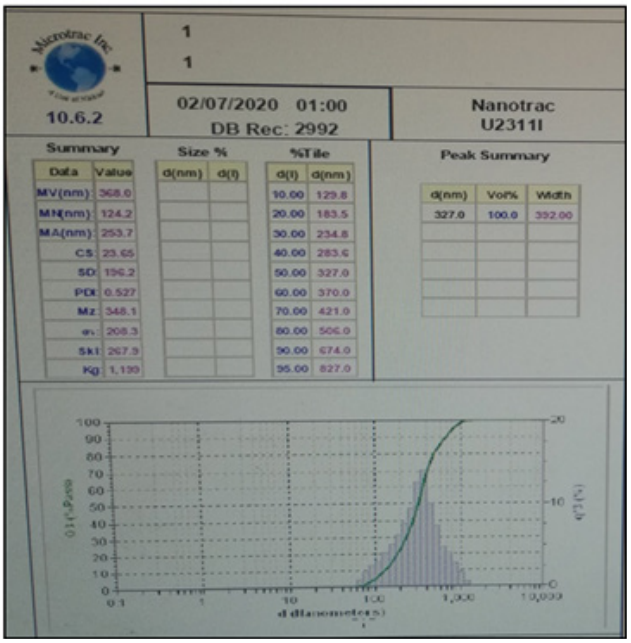

Figure 4: Particle size and PDI of Optimized phytosome formulation FS4.

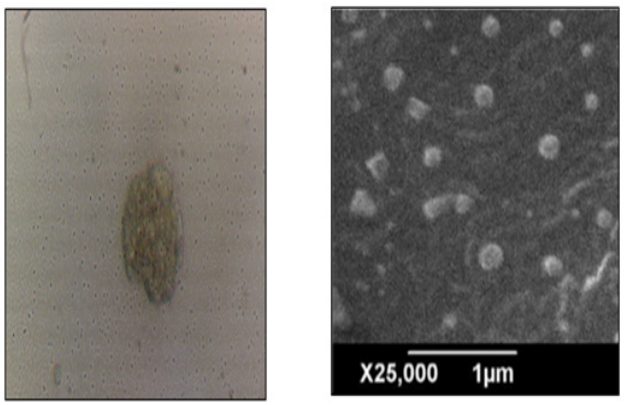

Figure 5: Vesicles Morphology of Phytosome formulation.

d) FT-IR Spectroscopy

Fourier Transform Infrared (FT-IR) technique is used to study the physical and chemical interaction between drug and excipients. FT-IR spectrum of pure alkaloid fraction, physical mixture of fraction with excipients and phytosomes was carried out to check the compatibility of drug after combining with the excipients by potassium bromide method (Figure 7).

Ex-vivo Intestinal Permeability Study[19-21]

Ex-vivo permeation study was performed by using non-everted gut sac method using chicken ileum, collected from nearby slaughter house. The separated two small segments were washed at room temperature six times with Krebs Ringer's solution together with continuous aeration. After washing, two segments of the ileum were filled with phytosomal suspension as well as aqueous raw alkaloid fraction solution. Such segments were tightened at both ends and placed under continuous bubbled with atmosphere air in a beaker containing 50ml of Krebs Ringer's solution. In order tomaintain the temperature at 37 ±0.5°C, the gut sac bath is enclosed by an outer water jacket. After 1 hr the all drug solution was withdrawn and release amount of alkaloid from *Tinospora cordifolia* was determined by estimation of total alkaloid content.

RESULTS AND DISCUSSION

Microscopic Study

Powder Microscopy

The powdered material of *Tinospora cordifolia* stem was creamish brown in color, odorless and slightly bitter in taste. Microscopy study of powder showed the presence

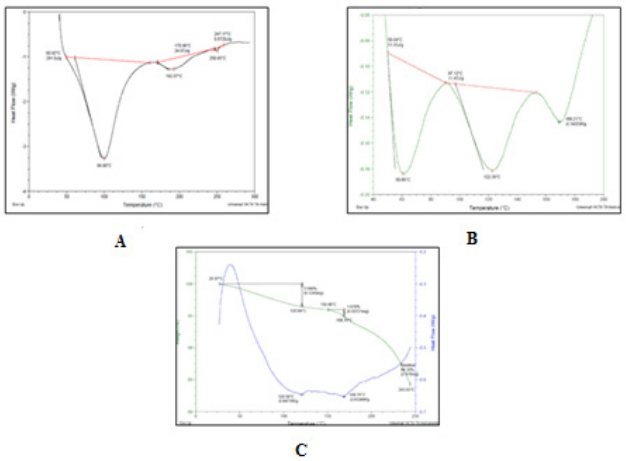

Figure 6: DSC of a) Fraction, b) Physical mixture, c) Phytosome.

of fibers which are lignified and long in shape. Tracheids with bordered pits and horizontal perforations. Xylem vessels cylindrical and bear bordered pits (Figure 8).

Physicochemical study

The physico-chemical investigation tests were performed to analyze the quality and purity of *Tinospora cordifolia*. Ash value is useful in determining the authenticity and purity of the plant material. The total ash, acid insoluble and water soluble ash value for *Tinospora cordifolia* was found in range of 10±0.6, 2±0.05 and 7± 0.25 respectively. The water soluble extractive value is higher than alcohol soluble extractive in *T. cordifolia*. The samples of alcohol soluble and water soluble extractive values were found within the range of 7±0.5 and 19±0.25 respectively. The major factor responsible for the deterioration of the samples is moisture. Low moisture is always desirable for greater stability of drugs. The loss on drying in *Tinospora cordifolia* plant were found within the range of 1.76 ± 0.04 (Table 1).

Preliminary phytochemical screening

The phytochemical screening of extract shows the presence of alkaloids, carbohydrates, terpenoids, tannins, steroids, flavonoids and phenols in the *T. cordifolia* extract. Saponins are absent in the extract (Table 2).

Determination of total alkaloid, phenol and flavonoid content

The total alkaloid, phenolic and flavonoid content was found to be 6.1 ± 0.001mgAE/g, 5.4 ± 0.05mgGAE/g, 3.6 ± 0.02 mg QE/g respectively in *Tinospora cordifolia* stem extract. Table 3 summarizes the data for determination of total alkaloid, phenolic and flavonoid content.

Table 1: Physiochemical investigation of *Tinospora cordifolia*.

Sr. No	Physico-chemical Parameters (%w/w)	Results for *Tinospora cordifolia* (%w/w)	Standard Value (% w/w)
1.	Total ash	10 ± 0.6	NMT 10 %
2.	Acid Insoluble ash	2 ± 0.05	NMT 3%
3.	Water soluble ash	7 ± 0.25	NMT 20%
4.	Alcohol Soluble Extractive value	7 ± 0.5	NLT 1.5%
5.	Water Soluble Extractive value	19 ± 0.25	NLT 9%
6.	Loss on drying	1.76 ± 0.04	NMT 10%

Results are presented as the mean±SD, (n=3)

Table 2: Preliminary Phytochemical Screening.

Phytochemical Test		Observation	*T. cordifolia* Extract
Alkaloid	Mayer's Test	Gives ppt	+
	Dragendorff's Test	Orange-Brown ppt	+
	Wagner's Test	Reddish-Brown ppt	+
	Hager's Test	Yellow ppt	+
Carbohydrates	Molisch's Test	violet ring formation at intersection of two liquids	+
Flavonoids	Shinoda Test	Orange, Pink, Red to Purple colour	+
	NaOH + Conc. H_2SO_4	NaOH – Colouration H_2SO_4 – Decolouration	+
Tannins	Lead Acetate Test	Yellow ppt	+
Terpenoids	Salkowski Test	Chloroform layer – Red colour Acid layer – Greenish yellow fluorescence	+
Steroids	LibbermannBurchard Test	Red, Blue to Green colour	+
Polyphenols	10% $FeCl_3$ Test	Blue / Green colour	+
Saponins	Foam Test	Foam formation	-

(+ = Present and - = Absent)

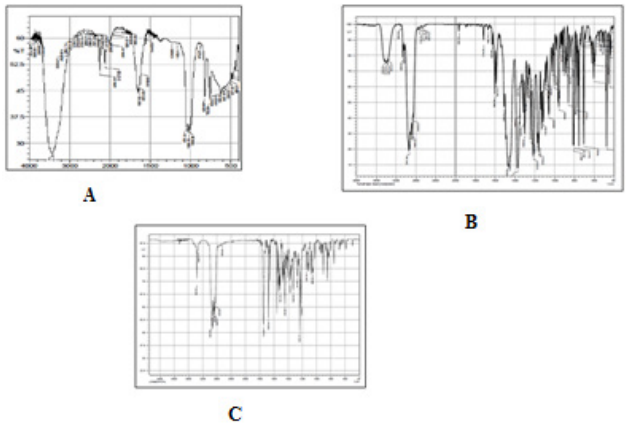

Figure 7: FTIR of a) fraction, b) Physical mixture, c) Phytosome.

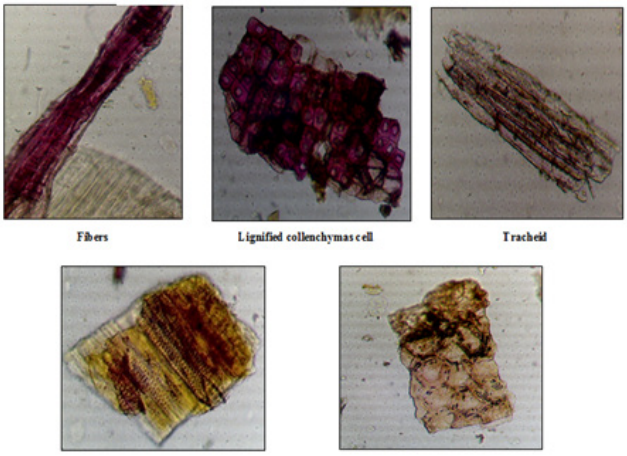

Figure 8: Photographs of powder microscopy of *Tinospora cordifolia* stem.

Table 3: Data for determination of total alkaloid, phenolic and flavonoid content.

Sr. No	Plant Name	Parameters	Results
1.	*Tinospora cordifolia*	Total alkaloid content (mg AE/g dry extract)	6.1 ± 0.001
2.		Total phenolic content (mg GAE/g dry extract)	5.4 ± 0.05
3.		Total flavonoids (mg QE/g dry extract)	3.6 ± 0.02

Results are presented as the mean±SD, (n=3)

Evaluation of Phytosomes

Particle Size

The particle size and polydispersity index (PDI) of phytosome was measured by Nanotrac Particle Size Analyzer. Particle size data and polydispersity index for prepared phytosome formulations FS1 to FS2 was listed in Table 5. Smaller particle size indicates better drug permeation and PDI indicates uniform size distribution of particles. The particle size of formulation FS 4 is 368 ± 0.12 and PDI was 0.5. So, Formulation FS 4 shows smaller particle size and PDI range which is used as optimized formulation for further study.

Vesicles morphology

Shape and surface morphology of phytosome formulation FS 4 was studied using Trinocular microscope and Scanning electron microscopy. Trinocular microscopy and SEM photographs of formulation FS 4 was shown in Figure 5. The phytosome formulation FS 4 was found to be smooth and spherical in shape.

Differential Scanning Colorimetry (DSC)

The obtained thermograms of pure fraction, physical mixture and phytosome formulation by Differential scanning Colorimetry (DSC) were Figure 6. The fraction in physical mixture showed the melting point within the range with no additional shift in endothermic peak which indicated that drug is compatible with other ingredient. The pure fraction exhibited sharp endothermic peak at 99.90°C.

FT-IR Spectroscopy

FT-IR spectroscopy was performed to study the compatibility of pure fraction and physical mixture of fraction with soya lecithin and phytosome formulation respectively. From the FT-IR spectra observed that characteristic peak of drug was present in the combination also. The reported peak frequencies were shown in Table 6. The functional groups are lies within the limit and there is no interaction between drug and excipients.

Ex-vivo intestinal permeability study

The *Ex-vivo* permeation study was performed with the help of everted gut sac method using chicken ileum. This study shows the linkage between drug absorption and drug permeation. Result of the study shows that the phytosome formulation (FS4) was more permeated within 1 hr because of incorporation of fraction inside the lipid matrix while permeation of fraction (F3) is less. The phytosome formulation (FS4) was found to be 1.85 times more permeable than the pure fraction (F3) (Table 7). The formulated phytosomes shows more potency in enhancement of drug permeability as compared to pure fraction of alkaloid from *Tinospora cordifolia*.

Table 4: Formulation Table of alkaloid loaded phytosome.

Sr.No	Formulation code	Drug (mg)	Cholesterol (mg)	Lecithin (mg)	Dichloromethane (ml)	Methanol (ml)	Water (ml)	Ethanol (ml)	Drug : Cholesterol : lecithin
1.	FS1	10	15	10	10	5	10	10	1:1.5:1
2.	FS2	10	15	20	10	5	10	10	1:1.5:2
3.	FS3	10	15	30	10	5	10	10	1:1.5:3
4.	FS4	10	15	40	10	5	10	10	1:1.5:4

Table 5: Particle size and PDI of vesicles.

Sr.No	Formulation Code	Particle Size (nm)	PDI
1.	FS 1	628± 76	0.7
2.	FS 2	587±0.85	0.9
3.	FS 3	554± 0.62	0.7
4.	FS 4	368± 0.12	0.5

Table 6: FTIR spectral data of pure fraction, physical mixture and phytosome.

Functional Group	Observed Frequencies		
	Pure Fraction	Fraction + excipients (Physical Mixture)	Phytosome formulation
N-H Strech	3316	3317	3227
C-O Stretch	1141	1714	1514.72
C-H Stretch	1482.95	2922	2995.68
C-C Stretch	1473	1437	1641.05
C=C Stretch	1514.22	1514	1516.12

Table 7: Data for *Ex-vivo* intestinal permeability Study.

Sr. No	Parameter	Result
1.	Alkaloid content of pure fraction (After permeation through ileum)	6.88 ± 0.69
2.	Alkaloid content of formulated phytosomes (after permeation through ileum)	12.77 ± 0.50

CONCLUSION

The above study conclude that alkaloid loaded phytosomes from stem of *Tinospora cordifolia* has better physical characteristics than crude alkaloid fraction. *Ex-vivo* intestinal permeability study revealed that the phytosome formulation shows more potency in enhancement of permeability of alkaloids incorporated in it than the crude alkaloid fraction.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

BCG: Bromocresol Green; **PDI:** Polydispersity Index; **SEM:** Scanning Electron Microscopy; **DSC:** Differential Scanning Calorimetry; **FT-IR:** Fourier Transform Infrared.

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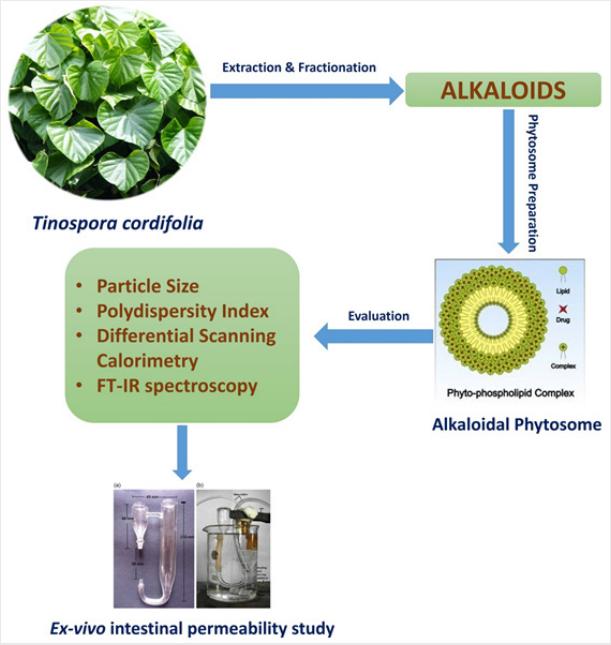
PICTORIAL ABSTRACT



SUMMARY

Phytosomes are newly introduced novel dosage form for improving the bioavailability and therapeutic effect of the herbal drug. In the present study preparation and evaluation of alkaloid loaded phytosome from *Tinospora cordifolia* was carried out. The hydroalcoholic extracts of *T. cordifolia* were screened for total content of phenols, flavonoids and alkaloids. A total four Phytosome formulations were prepared by using thin film hydration method with different ratio of soya lecithin and cholesterol. Further evaluation of phytosome was carried out. The *ex-vivo* intestinal permeability study was performed for crude fraction and prepared phytosome to assess the intestinal permeability enhancement. The all standardization parameters showed the results within the standard limits, thus confirming the quality and purity of raw material. The particle size and polydispersity index was found within the acceptable limits. In *ex-vivo* permeability analysis of the intestines study was found that the phytosome shows enhancement in intestinal permeability than the crude alkaloid fraction. The above results indicated that the prepared alkaloid loaded phytosome shows promising potential in enhancement of intestinal permeability of *Tinospora cordifolia*.

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