IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
December 2022 Vol.:26, Issue:1

Phytosomal Nanotechnology Platform for Various Formulations of *Glycyrrhiza glabra*

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ISSN 2349-7203
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Submitted: 24 November 2022
Accepted: 30 November 2022
Published: 30 December 2022

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Phytosome, Novel Drug delivery system, skin disorder, Liquorice

ABSTRACT

Review of Phytosome of Herbal drug deals in Novel Drug Delivery System because of its easy bioavailability, less side effect and cost effectiveness. Much herbal medication can be use in the form of Phytosome which is better in absorption. Skin disorders, skin ageing and skin pigmentation and diseases may treat through phytosome drug delivery. Phytosome is cell like structure complexes with Phosphatidycholine and can be prepared by many other methods but mostly prepared by "Solvent Evaporation Method". This article shows Preparation, approaches of novel drug delivery and evaluation standards for Phytosomes. Phytosomes are the advanced formulations for herbal constituents, as the phytosome quickly absorbed they show better results. There is vast use of Liquorice (mulethi) as a traditional medicine in cosmetic products to treat the skin disorders. In this article there is an overview about chemical constituents and pharmacological actions of Glycyrrhiza glabra linn. (Family – Fabaceae). It is also known as Yashti Madhu.

INTRODUCTION

Glycyrrhiza glabra linn. is also called Yashti Madhu. Liquorice have been reached down in therapeutics for more than 4000 years. It is used as antifungal, anti-inflammatory, anticancer, antioxidant, anti-ageing, anti-diabetic and useful to treat the skin disorder.

Glycyrrhizin is vital functioning component acquired from Glycyrrhiza root, by and large traditional drug in botanical preparation for the medical care and superintendence of persistent disease.

Glycyrrhiza glabra is known as Liquorice and sweet wood with family Leguminaceae. Liquorice has make use of a part of pharmaceutical for over 4000 years. Glycyrrhiza glabra can call liquorice and sweet wood, is significant for sugary and rhiza, which defines root. Generally, the withered rhizome and centre of the plant have being put to use alleviative by the Egypt, China, Greek, India and Roman human evolution as an anti-tussive and demulcent.

Glycyrrhiza glabra is a sturdy shrub, tall up to 2.5 meter. Leaves of Glycyrrhiza posses 4-8 pairs of ovoid or lancelet leaflets. Flowers of Liquorice are slender usually lavender to violet in colour. The calyx is tiny and having glandulous hairs. Fruit is flattened herb or shell up to 1.5 cm long. The fibrous root is around 1.5 cm long and bisected in 3-6 aid roots. These may achieve 8 meter.

Liquorice extracts are continuously utilized as a flavouring agent to conceal astringent taste in positioning, and as an expectorant in glacial preparations.

PHARMCOLOGICAL ACTIVITY:-

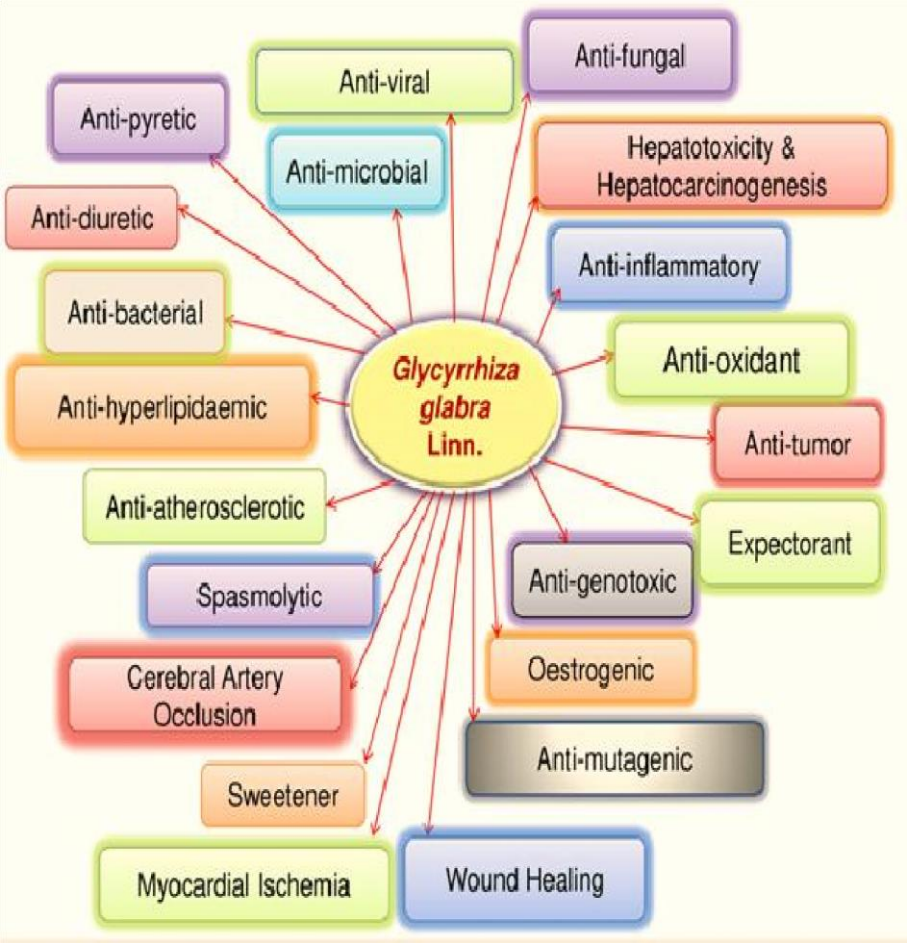

Fig 1: Pharmacological Activity of drug

Tab: 1 composition of Glycyrrhiza glabra and therapeutic use

S.N.	Composition	Therapeutic Use
1	Glycyrrhiza extract	Use in irritating cough. antitussive, chronic inflammatory condition of air passage
2	Glycyrrhiza glabra extract	Antioxidant support
3	1 ml. Liquorice liquid: Liquorice extract (1:3)	Dry cough and promote clear breathing
4	Liquorice , gelatine and magnesium stearate	Health supplement
5	Liquorice root 790 mg	Supports the glandular system
6	Glycyrrhiza glabra (0.2) ml	Used as Expectorant in bronchitis
7	Deglycyrrhizinated Liquorice 380 mg	Health Supplement
8	Organic liquorice root 250 mg.	Gastric support soothes the mucous membrane
9	Glycyrrhiza glabra root extract	Claims to whiten, brighten underarm area
10	Garden chrysanthemum, aloevera and liquorice root	Face cleanser
11	Pomegranate, saffron. liquorice	Removes dark spot
12	Retinol, Liquorice	Antiaging cream

PHYTOSOME

Phytosomes take place as NDDS carried hydrophilic functionalized phytoconstituents of savoury hurdle by phospholipid.

Phytosome belongs to a Greek term “Phyto” meaning to plant and “some” meaning cell like.

Phytosomes have to more bio available when differentiated with conventional botanical extract inferable to their upgraded ability to rood the lipoid bio film and eventually came to movement of blood. The Phytosomes innovation creates a little cell, well capable of travel from a water soluble domain within the lipophilic biological environment of the entrecote membrane of cell at last get to the blood. In such way, it makes certain the safely delivering the significant parts of the Phytoconstituent from abolish by digestive secretion and gut

bacteria. Phytosomes are designed when the solitary components of an herbal extract are destined to phosphatidycholine (derived from soy).

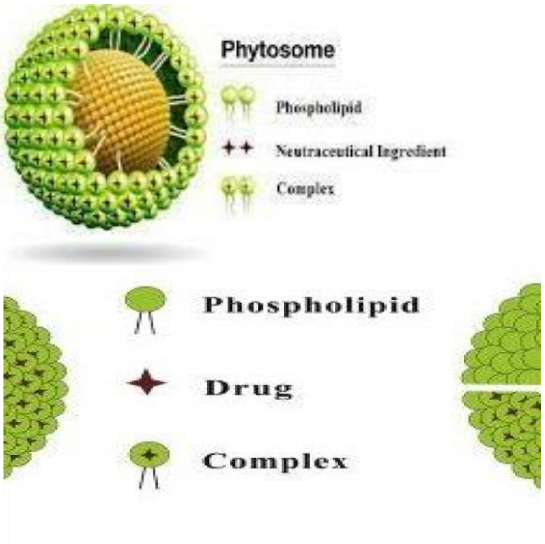

Fig 2: phytosome

PHOSPHOLIPID

Phosphatidycholine (PC) is a phospholipid, a huge organic particle that is a common building block for cell membranes. Phosphatidycholine has contrasting characteristics that upgrades its accessibility as a nutritive supplement. PC is additionally guarded and entirely compatible with pharmaceuticals and with other nutrients. It is likewise completely bio available (around 90%of administered quantity is absorbed over more than 24 hours) and it is a great emulsifier that elevations the bioavailability of supplements with which it is Co administered. Phospholipid has a water soluble head and water insoluble tail.

PHYTOSOME technology has breakthrough model for:-

- Remarkable prominent medicinal welfare.
- Assertive reach to the tissue.
- No compromise of nutrient safety.
- Marked enhancement of bioavailability.

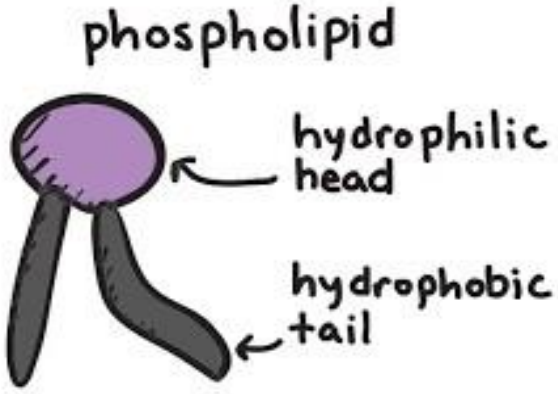

Fig 3: Phospholipid

ADVANTAGE

- Topical preparations avoid the GI-irritation.
- It avoids first pass metabolism.
- Enhanced absorption of herbal constituent.
- When soaking up of agile constituents has upgraded, need of dose decreased.
- It shows better stability profile.
- Convince actual transporting of drugs in particular place.
- Entrapment efficiency is high.
- Phytosome is greater than liposome, when use in topical preparation.
- Superior bioavailability.

Method of Preparation of Phytosome

1. Solvent Evaporation Technique
2. Mechanical Dispersion Technique
3. Salting Out Technique
4. Lyophilization Technique

SELECTION OF PHYTOSOMES CONTAINING DOSAGE FORM

Phytosomes formulation may be transport by both routes like oral and topically, to get the greater output regarding bioavailability of the phytosomes.

Soft gelatine capsule:

These kind of phytosomes which are formulated in form of suspensions with phytoconstituents as dispersed phase like vegetable oils or semi synthetic oils as dispersion medium it is use to construct soft gelatine phytosomes capsules for oral drug delivery.

Hard gelatine capsule:

It may be filled into hard gelatine capsules in powder form independently. Capsule size cannot have increase 300 mg for low density phytosomes.

Tablet:

A Phyto-phospholipid complex powder do not in any way have great properties due to their potential stickiness, flow ability, and have low density. The tablet is make with compression then drug is mixed 80-90% with other ingredient. Dry granulation process is the much suitable for the dose uniformity and convenient bioavailability.

Topical dosage form:

Phyto-phospholipid complex may formulate topically in form of cream, gel, ointment. It is innovative process to incorporate the phytosomes complex and mixed with oily phase in little amount and dispersed in an emulsion at temperature (not more than 40°C). In case outside part is water containing part then the phytosomes compound might also by dispersed into the watery phase and again added final formulation under 40°C.

Tab: 2 Application of different phyto phospholipid complexes in market

S.N.	Marketed Product (Phytosome)	Phytoconstituent complex	Application
1	Silybin	Silymarin by silybin	Provide antioxidant defence in skin and liver
2	Grape seed	Vitis vinifera	In treatment of cancer, antioxidant
3	Curcumin	Curcuma longa (polyphenols)	Used in the treatment of cancer
4	Centella	terpenes	Skin and vein disorder
5	Howthorn	Flavonoids from crataegus sp	Nutraceuticals
6	Zanthalene	Zanthoxylum bungeanum	Soothing, antiirritant, anti itching
7	Oleaselect	Polyphenols olive from oil	Used to reduced swelling
8	Sabaselect	Extract of saw palmet to berries	Provide normal function to prostate

MATERIAL AND METHOD

EXTRACTION OF LIQUORICE

1. Thimble is prepared to fill the herbal drug powder.
2. Heat is provided to the solvent.
3. The process of extraction is continually repeated.
4. Extraction is completed.
5. Extract is collected into the distillation flask.
6. Repeat the process until the liquid is become colourless.

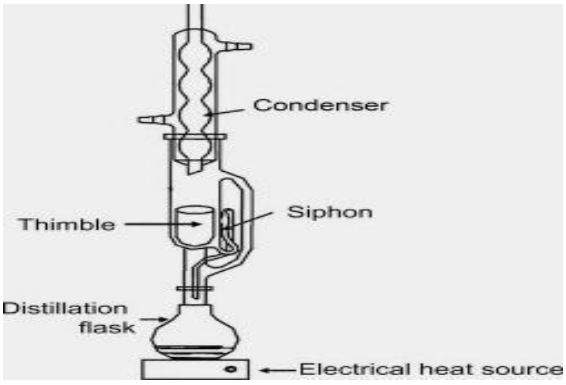

Fig 4: Extraction of Drug through Soxhlet Assembly

ISOLATION OF EXTRACTION

1. Extract has concentrated under reduced pressure.
2. It processed in vacuum rotary evaporator.
3. Extract dried in Hot Air Oven.
4. Until the semi solid concentration is obtained.
5. Stored in air tight container.
6. Kept in refrigerator.

PREPARATION OF PHYTOSOME

Phytosome of Liquorice is prepared by "Rotary Evaporation Method".

MATERIAL

Chemical reagents and equipment used in the preparation of Phytosome listed below.

S.No.	MATERIAL	EQUIPMENT
1	Liquorice	Digital Balance
2	Soy lecithin	Boiling Point Apparatus
3	Dichloro methane	Franz Diffusion cell
4	N Hexane	Soxhlet Apparatus
5	Phosphate Buffer	Heating mental
6	Ethanol	Rotary Evaporator

EXTRACTION AND BIOLOGICAL ACTIVITY OF ROOT EXTRACT Soxhlet Apparatus

1. Thimble is packed with powdered drug of liquorice.
2. Placed in the main chamber of Soxhlet apparatus.
3. By heating the solvent, it started boiling and evaporated.
4. Through the condenser evaporated drug has condensed and dropped into the flask by the way of Siphon tube.
5. This process is repeated many times.
6. The soluble constituent are extracted,
7. This process is continued until the powdered drug is completely extracted and the colour of the thimble becomes colourless or faded.

Fig 5: Thimble of Liquorice powdered drug

EXTRACTION

Glycyrrhiza glabra Ethanolic extract

Root of Glycyrrhiza glabra has been washed completely with water and dried. Dried root have being powered by using cutter mill and sieved by sieve (no. 80) to obtained the same size of drug. The powder was extracted in Soxhlet apparatus, 25 Gms of powdered root has stuffed in the Soxhlet then ethanol employ as solvent. Ethanol has filled until one siphon completed. Soxhlet was runned nearly for 7-8 hours at different average temperature. Then

extract has concentrated to dehumidify under reduced pressure 40*C in vacuum rotary evaporator. After that the drug has to be dry in hot air oven and stored in an air tight container then kept in a refrigerator.

Fig 6: **Soxhlet Assembly of Liquorice root Extraction**

1) Phytochemical Screening of Extract Saponins test

Flavonoids test

With sodium hydroxide-

With sulphuric acid- Shinoda test-

Lieberman's test- for terpenoids

Fehling's test

Solubility profile of Liquorice

The solubility profile is purposely depending upon the type of solvents like acetone, ethanol, methanol, and dichloromethane and phosphate buffer.

2) **UV spectral analysis**

A solution (Liquorice) of 100µg/ml is made firstly, then it can be obtained under UV spectrophotometer within range 100-800 nm. Then the UV spectrum is formed.

3) **Compatibility Studies**

In compatibility test both the drug (Liquorice) and phospholipid (Soy lecithin) can compared for the chance of any type of physiochemical reaction and it can be defined by FTIR spectroscopy.

RESULTS AND DISCUSSION

Observation found through phytochemical test

Tab: 3 Observation found through phytochemical screening

S.N.	TESTS		OBSERVATION	INFERENCE
1.	Fehling Test		Brick red precipitate	+
2.	Flavonoids test	With the sodium hydroxide	Yellow colour	+
		With H2So4	Orange to red colour	+
		Shinoda test	Magenta to purple colour	+
3.	Test for Saponins		Foam recognised for some time	+
4.	Terpenoids test	Lieberman‟s test	Showing pink shade	+

Solubility profile of Liquorice Extract:

Liquorice has been recognized soluble in phosphate buffer and dichloromethane. And the suitable solvent for liquorice which is used in this experiment is Ethanol.

UV Spectral Analysis

Spectral analysis of Liquorice has been determined by UV spectrophotometer. The highest peak is found 230 nm and the standard peak is found 254 nm.

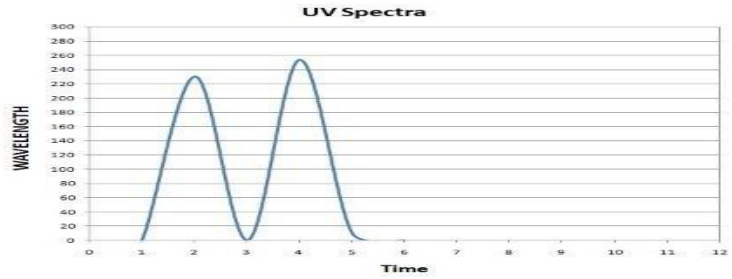

Fig 7: **UV Spectra of Liquorice extract**

Compatibility studies

In compatibility test both the drug (Liquorice) and phospholipid (Soy lecithin) can compared for the chance of any type of physiochemical reaction and it can be defined by FTIR spectroscopy.

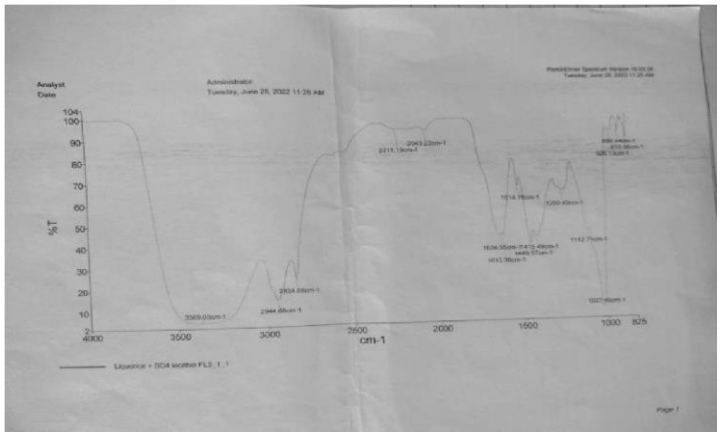

Fig 8: Compatibility between drug and phospholipid

PREPARATION AND EVALUATION METHOD OF PREPARATION ROTARY EVAPORATOR TECHNIQUE

This method is used to remove solvent from solute and formation of a film. Firstly boiling flask is attached to the rotating rod. Paraffin wax is applied to the mouth of rotating flask. Flask touch to the cool water level. Switch on the apparatus. RPM is adjusted to 100 rpm. Temperature does not exceed from 40*C. The time of the evaporation process is approx. 20 minutes. And after that film formation has been started.

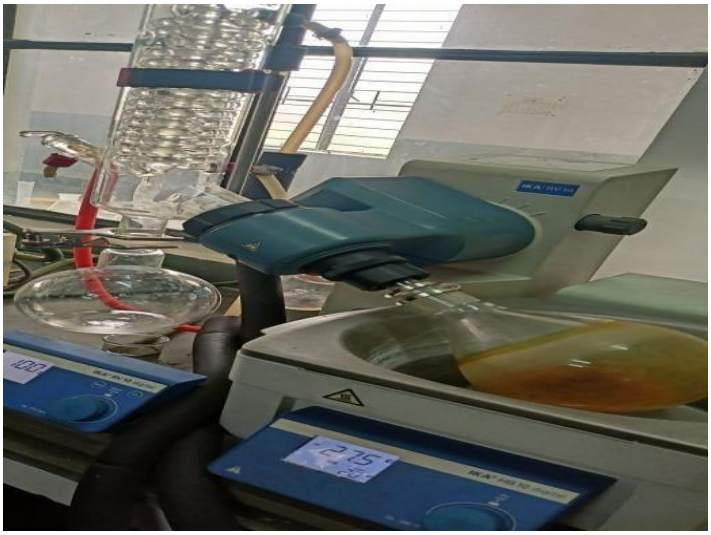

Fig 9: Rota Evaporator with Liquorice Extract

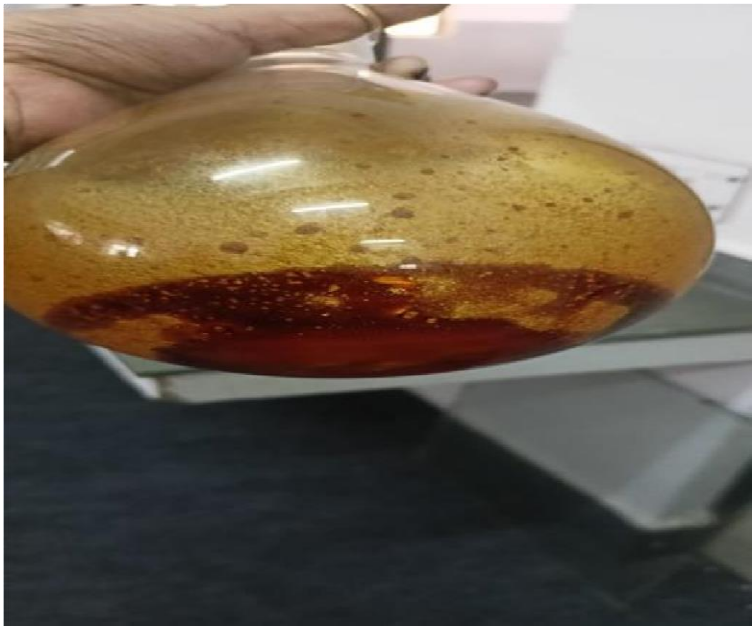

Fig 10: Film formation of liquorice Extract

Preparation of Liquorice Phytosome

Phytosomes complex of Liquorice has prepared by Rotary Evaporator method in the ratio of (following by table) by different polymer concentration.

Formulation Table

Tab: 4 Formulation Table

S.N.	Formulation Code	Ratio of Drug: Soy lecithin	Dichloromethane	Hexane	Phosphate Buffer
1	FL1	1:1	20 ml.	15 ml.	5ml.
2	FL2	1:2	20 ml.	15 ml.	5ml.
3	FL3	1:3	20 ml.	15 ml.	5ml.
4	FL4	1:4	20 ml.	15 ml.	5ml.
5	FL5	1:5	20 ml.	15 ml.	5ml.

Fig 11: Formulation of Glycyrrhiza glabra Phytosome (FL1-FL5)

EVALUATION OF PHYTOSOME

Visualisation of Phytosome

The morphology of phytosomes has observed by digital microscopy.

Microscopy (Digital)

The structure of the phytosome of Liquorice can be seen under the digital microscope approx range 400X.

Percentage yield

Percentage yield of the formulation can be measured with this formula.

Percentage yield = practical yield X theoretical yield (100)

Efficiency for entrapment

Phytosome of Liquorice has centrifuged at 10000 rpm for 30 minutes. And it is done by Remi centrifuge. Then the separate drug observed under UV spectrophotometer. to know the entrapment efficiency of drug following formula has been used.

$$\text{Entrapment efficiency of drug} = \frac{\text{Amount of drug} + 100}{\text{Amount of drug added}}$$

Drug Content

In this evaluation test 100 ml of drug is dissolved in methanol and when the drug is completely dissolved then the absorbance can be check under UV Spectrophotometer at 254 nm. Drug content has been determined by using this method.

FTIR

FTIR test has been done to collect the spectral data of the preparation. And this data is helpful to know about the structure of drug and chemical stability of drug. The range of Spectral scanning is must be approx between 4000 and 300 cm^{-1}.

Visualization Digital Microscopy

The structure of the phytosome of Liquorice can be seen under the digital microscope approx range 400X.

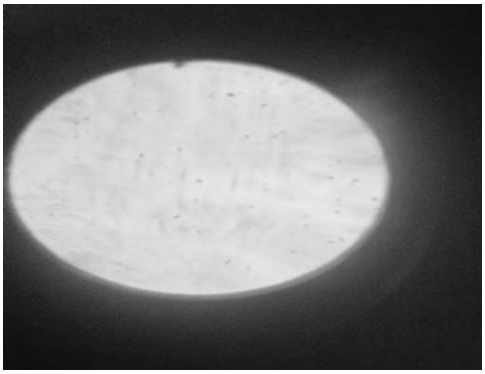

Fig 12: Microscopic visualization of phytosome of Liquorice Extract

Percentage yield, Drug Content and Entrapment Efficiency

The phytosome of Liquorice formulation FL5 has maximum range of percentage yield, entrapment efficiency and content of drug. In formulation (FL1- FL5) range of percentage yield is found to be 70-88%, the drug content percentage range is found to be 70-87% and the range of entrapment efficiency is found to be 75-87% respectively.

Tab: 5 Table of % yield, %drug content and entrapment efficiency

S.N.	FORMULATION	PERCENTAGE YIELD	%DRUG CONTENT	ENTRAPMENT EFFICIENCY
1	FL1	70.27	72.98	75.94
2	FL2	74.65	82.43	80.21
3	FL3	80.90	86.84	82.56
4	FL4	85.84	87.64	85.40
5	FL5	88.54	87.90	86.61

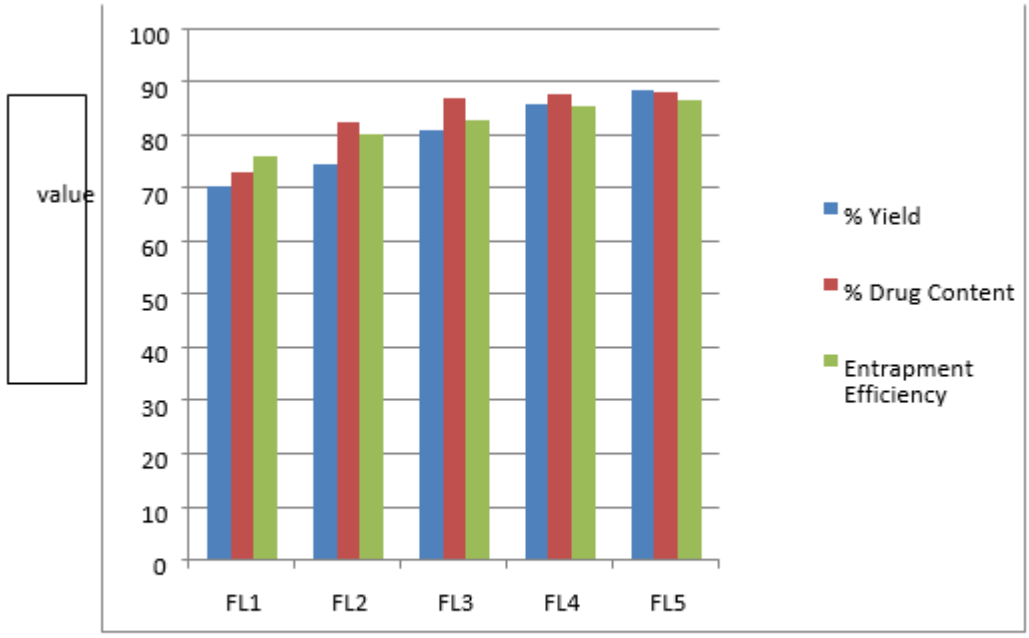

Fig 13: chart of % yield, % drug content, Entrapment efficiency

FTIR

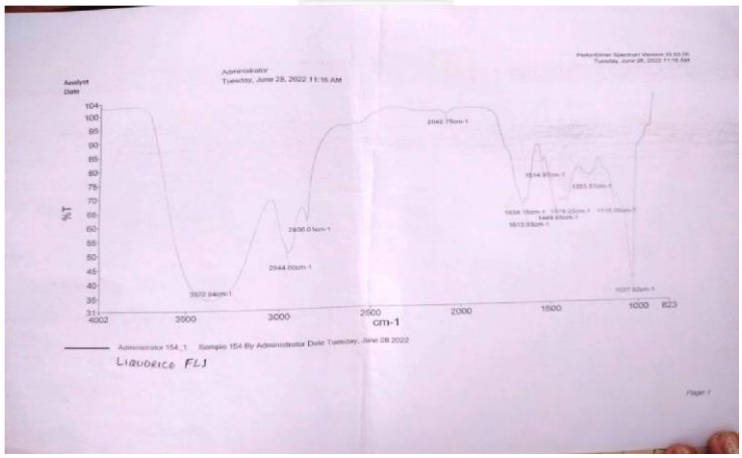

Fig 14: IR spectra of Liquorice

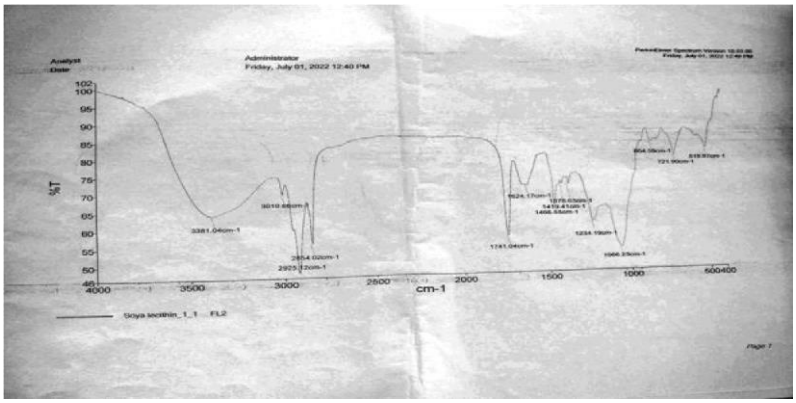

Fig 15: **IR spectra of Soy Lecithin**

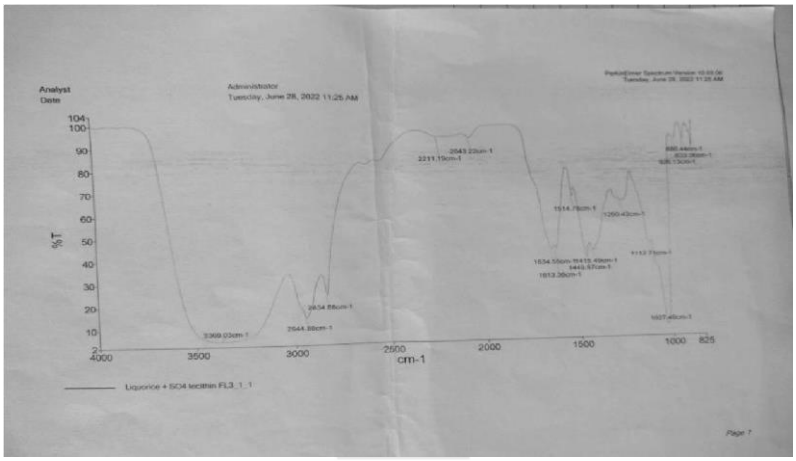

Fig 16: IR spectra of Liquorice Phytosome

In VITRO Test

Liquorice phytosome which is prepared placed in a diffusion cell and PBS is filled in receptor compartment. The temperature of diffusion cell is 37^{o}C.

5 mg phytosome taken from all the formulation. In FL5 formulation drug release is found 76.12%. Liquorice drug in vitro release shows very rapid release and then released very slow. Initially fast release of drug shows that the active drug is cumulated on the surface of Phytosome.

In Vitro Drug Release

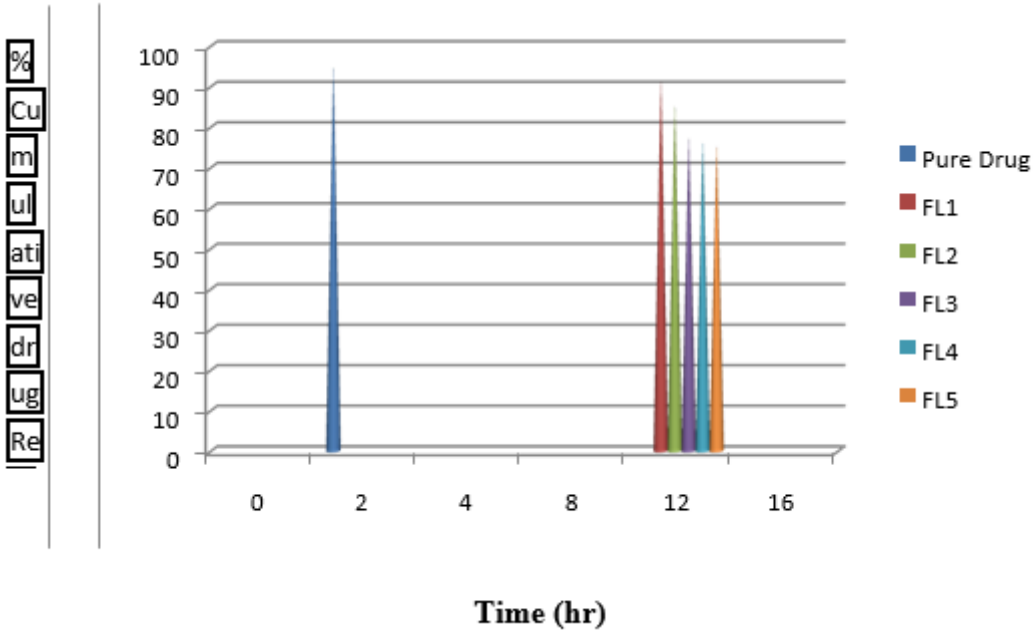

Fig 17: Chart of In Vitro Drug Release

Release Kinetics

All the formulation (FL1-FL5) has being fitted in different kinetic model and release profile.

It has been showed that each formulation follows zero order, first order and Highuchi plot.

Tab: 6 Release kinetics chart of zero order, first order and Higuchi Plot

S.N.	Formulation Code	Zero Order	First Order	Higuchi Plot
1	FL1	0.836	0.974	0.935
2	FL2	0.875	0.980	0.971
3	FL3	0.876	0.972	0.962
4	FL4	0.877	0.964	0.956
5	FL5	0.890	0.963	0.946

Stability Studies

Liquorice phytosomes have being kept reserved in refrigerator and at the room temperature both. After 1 month release of drug, drug content has been observed. in all the formulation, FL5 shows greater release of drug and stability. Results of this study have been done to know

any type of change if persist at refrigerator temperature and room temperature. at the end of the study the formulation does not show any type of change or degradation on storage. Thus, liquorice phytosome is a stable preparation.

Tab: 7 Stability of (FL5) formulation

Parameter	**Room Temp.**	**Oven Temp.**	**Cold Temp.**
Appearance	No change	Slightly change	No change
Homogeneity	No change	Slightly change	No change
Viscosity	No change	Decrease Viscosity	No change

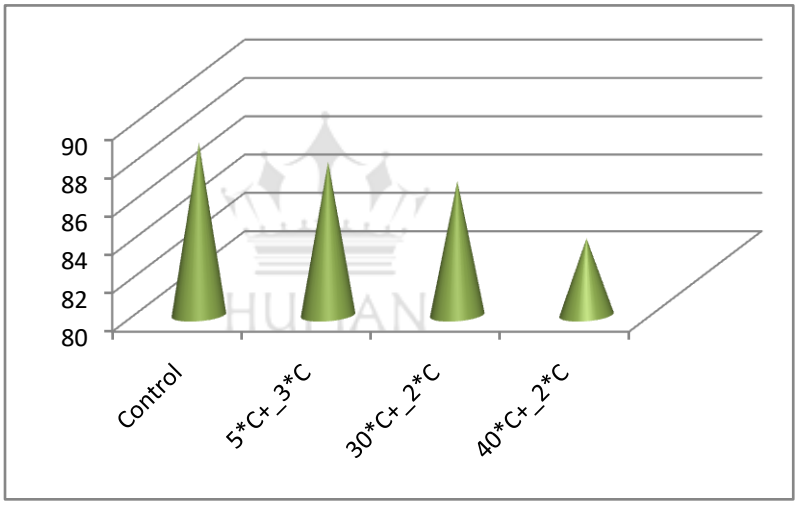

Fig 18: Stability Studies of optimized formulation (FL5) at different temperature after 15 days approx.

CONCLUSION

Liquorice phytosome constituted by Rotary Evaporation method.

As explained above that liquorice has so many pharmacological activities and if liquorice extract is converted into phytosome formulation, then the bioavailability and stability, drug release is enhanced.

The entrapment efficiency is also increase of the drug is in the form of phytosome and then polymer concentration is also increased.

This study is observed that the finest method to prepared phytosome is Rotary Evaporation Method.

Stability studies of the phytosome formulation have been accomplished fir the liquorice formulation (FL5).

After all the evaluation studies like release kinetics, drug content percentage and entrapment efficiency of the drug and In vitro drug release is also studied and found that liquorice phytosome is much suitable for the different formulation.

The stability of the liquorice phytosome is also long lasting. It does degrade neither at refrigerator temperature nor at room temperature.

Phytosome of Liquorice with ratio (1:5) has observed to be effective and capable for drug delivery.

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