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Original Article

DESIGN AND DEVELOPMENT OF PHYTOSOMAL SOFT NANOPARTICLES FOR LIVER TARGETING

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ABSTRACT

Objective: The objective of the study was to design and formulate ferulic acid (FA) phytosomes converted in to functionalised soft nanoparticles by using the solvent evaporation method to increase resistance time, improve the bioavailability and half-life of ferulic acid.

Methods: FA is a BCS-II drug, which has low solubility and high permeability. The functionalised soft nanoparticles was prepared by the solvent evaporation method followed by the particle size and zeta potential, Fourier Transform Infra-Red (FTIR), Powder x-Ray Diffraction (PXRD), Scanning Electron Microscope (SEM). It indicates good result for the complexation rate. PXRD showed good powder diffraction results with having good flow property. Particle size and zeta potential had a good result of-12.05±120 improved by the cationic polymer. The complex was evaluated by the study of drug loading, entrapment efficiency, histopathological study and mucoadhesive property for the final formulation of the microspheres system. Also, the formulation were evaluated for the *In vitro* drug dissolution study for rate of the extent of drug release. *Ex-vivo* drug diffusion study by using goat nasal mucosa using pH 6.6 for evaluating rate of the extent of drug diffusion through nasal mucosa.

Results: The results of the characterization studies indicated the designing of functionalised phytosomal soft nanoparticles (FPSN). The FPSN particle size and zeta potential had a good result of-12.05±120. The FTIR spectra of the complex showed a characteristic peak at 3652.8 cm^{-1}(OH-stretching) which indicate that the shifting and interaction between the FA and soya phospholipid complex (SPC 3). The P-XRD, SEM, *In vitro* dissolution showed good powder diffraction results with having good flow property. The complex is evaluated by the study of drug loading. Also formulation were evaluated for the *In vitro* drug dissolution study for rate of the extent of drug release. The result of the above studies was Drug loading increased at 44.42 %. The *Ex-vivo* permeation study ferulic acid-phytosomal soft nanoparticle (FALC-PSN) showed characteristic in the drug diffusion at 80.04 %, which indicate that the drug had increases its aqueous solubility and also change with the structural morphology.

Conclusion: It can be concluded that the ferulic acid phytosomal soft nanoparticles (FAPSN) enhance the solubility of the FA and increased the bioavailability and retention time to target liver cancer.

Keywords: Ferulic acid, Conjugation, Complex formation, Solvent evaporation technique, Nanoparticle, Drug targeted systems, Bioavailability

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INTRODUCTION

Ferulic acid (FA) IUPAC name: (E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoic acid), an antidiabetic, anticancer and pulmonary protective effect is used in the management of neurodegenerative disorder. FA exhibits a short half-life, rapid metabolism, and elimination [1].

The unsaturated side chain, phenolic nucleus, hydroxyl and methoxy groups linked to the phenyl ring, which eventually provides structure stabilisation via resonance, are responsible for FA's antioxidant effect. FA has been extensively employed in the food and pharmaceutical industries due to its low toxicity. Despite these potential medical uses, oral administration of FA results in limited absorption, rapid metabolism and elimination [2].

FA exhibits an absorption profile from the gastrointestinal tract when administered using traditional administration devices since it is a BCS class II medication (low solubility and high permeability). Therefore, we must create innovative and clever nanocarriers that can enhances the biopharmaceutical parameters of FA [3]. Additionally, FA is found in Chinese medicinal plants such Angelica sinensis, Cimicifuga racemose and Ligusticum chuanxiong. FA was proposed as a novel antioxidant compound with a strong cytoprotective activity due to both the ability to scavenge free radicals and activate cell stress response. However, the unfavourable pharmacokinetics, which reduces the bioavailability of FA after ingestion (or oral administration) and the restricted number of clinical studies carried out with the purpose of proving FA efficacy and safety, limited the evidence regarding the potential interest of this phenolic acid in humans [4].

The most prevalent FA metabolites in plasma are glucuronide (3–20 %) and sulfoglucuronide (60-90 %). According to both preclinical and clinical research, only a small amount of unmodified FA (9-20 %) has been discovered [5]. The kidney is primarily responsible for excreting FA and its metabolites. In contrast to humans, it is significantly slower and reaches a plateau between 7-9 h after consumption. The Urine excretion of FA in rats is quick and reaches a plateau 1.5 h after delivery. However, only 4-5 % of the ingested FA is retrieved unaltered in urine; these findings hold true for both humans and rodents [6].

The Apoptosis induction and inhibition of tumor cell proliferation are the approaches engaged in the treatment of cancer. Anti-cancer agents exhibit high toxicity to the tumor cell and also to the normal cells of the body where cancer developed [7].

Cancer is one of the leading causes of human sickness or diseases and deaths around the globe, competing for 7.6 million deaths per year. There are several types of cancer, and they vary depending on cancer location, size and various other parameters [8].

Different formulation strategies have been reported so far to improve liver cancer treatment. In 1970, Kopeck and colleagues created the first synthetic polymer-drug conjugates that was undergo clinical trials. Later to this in 1975, Rings Dorf was the first to propose the concept of polymer-drug conjugates. The purpose of polymer-drug conjugation was to improve medication targeting to the tumour lessen drug toxicity (by restricting access to the areas of toxicity) and circumvent drug resistance mechanisms. Doxorubicin, camptothecin, paclitaxel and platinates like carboplatin and diamino cyclohexane (DACH)-platinates are the first-generation conjugates that aim to increase the therapeutic index of medications currently in frequent clinical use. Hydrophobic medicines like doxorubicin and paclitaxel are more water soluble by conjugation to hydrophilic

polymeric carriers, making formulation and patient administration simpler. The fundamental building blocks of nanoscience and nanotechnology are nanomaterials.

A "nanomaterial" is a manufactured or described material that contains unbound, collected, or agglomerated particles with outer measures between 1-100 nm size [9]. A lot of targeting molecules have been developed using sugars, such as nanoparticles with galactosamide on their surfaces. Galactosylated nanoparticles interacted specifically with HepG2 cells through ligand-receptor (ASGP-R) recognition, according to cellular uptake research employing rhodamine 123 loaded nanoparticles with conjugated galactosamine [10].

The many types of nanoparticles come in spheres, cylinders, cubes, triangles, rings, or discs and come in a variety of sizes, forms, and dimensions. The techniques for preparing Different researchers have reported a variety of approaches up to this point for creating solid lipid nanoparticles (SLN). There are several ways available for making drug-loaded nanoparticles. The techniques include manufacturing of nanoparticles as supercritical fluid (SFEE), solvent evaporation, solvent\emulsification, or diffusion etc [11].

In the present study developed FA-PSN using galactose was selected as the carrier polymer and employed in the nanoparticle formulations at various drug/polymer ratios. The FA-PSN was characterized for drug loading, solubility, particle size and zeta potential, SEM, FTIR, and P-XRD, *in vitro* drug release, *Ex-vivo* permeation studies.

MATERIALS AND METHODS

FA was gifted by Yucca Enterprises, Mumbai India. Galactose (GTE), soya phospholipid complex LIPOID®(SPC-3), Di Methyl formide (DMF), Methane sulfonic acid, Ethanol, N-hexane, Dichloromethane, Sucrose was purchased from Ozone® International, Ahmedabad, India.

Method of preparation

Excipients: LIPOID®SPC-3, GTE, methane sulfonic acid, DMF, ethanol, distilled water in various concentration of polymers is taken in consideration to find check their compatibility and solubility while developing conjugation of galactose with FA [12].

Conjugation of GTE with FA

The prepared conjugation of GTE with FA was prepared. Briefly, the GTE ~200 mg and FA ~50 mg was accurately weighed and dissolved in 10 ml of DMF. The obtained solution was mixed with 0.1 ml of methane sulfonic acid. Prepared solution mixture was heated on water bath at 60 °C for 24 h. after heating, the dry residue was mixed with cold water forming precipitation of product. The product was filtered using Whatman filter paper and dried at room temperature [13].

Complex of conjugation and lipid

Accurately weighed the necessary amount of ethanol, LIPOID®SPC-3, and conjugation (30 ml) After adding (200 mg) LIPOID®SPC-3 using a sonicator to ethanol in a round bottom flask (RBF), and after adding (100 mg) conjugation to create a clear solution, the clear solution was kept for synthesis using a condenser assembly for two hours at 50 °C. After two hours, the solution was transferred into a china dish and kept in a heating water bath to evaporate the liquid. N-hexane was then added to the solution, allowed to dry, and used to collect the powder in a valve [14].

Preparation of phytosomal soft nanoparticles

Nano precipitation method for making PSN Briefly, 100 mg of FA complex were precisely weighed, combined with 15 ml of dichloromethane using a magnetic stirrer to create a transparent solution, and then added dropwise (0.2 ml/min) into distilled water in the presence of magnetic stirring (40 ml). When the dispersion phase was gradually evaporated while being stirred, FA-PSN and a suspension FA-PSN with a light yellowish opalescence were produced. The resulting suspension was then freeze-dried using a lyophilizer after adding 5 % sucrose w/w in solution as a stabilizer [15].

Physico-chemical characterization of optimized FA-D GAL

Particle size and zeta potential

Photon cross-correlation spectroscopy (PCCS) and dynamic light scattering were used to analyse the Ferulic acid D-galactose (FA-D GTE) particle size distribution. 10 ml of deionized water and 5 mg of FA-D GAL powder were combined in a sample container. In the sample chamber of the analyzer, the sample vial was manually inserted (Model: NANOPHOX, Sympatec Gmbh, Clausthal-Zellerfeld, Germany). Range: 1 nm to 10 nm. The sample vial positioning was designed to maximise the count rate using the appropriate software. The temperature was maintained at 25 °C for the duration of the measurement. The zeta potential of the FA-D GTE powder was evaluated using a dynamic light scattering (DLS) zeta potential and nanoparticle analyzer (Model: Nano plusTM-2, Particulate Systems) [16].

Scanning electron microscopy (SEM) analysis

Approximately 5µg/ml suspension of FA and FA-D GAL transformed to a cover slip, which in turn was mounted on a specimen tab. The sample were allowed to dry at room temperature. Then the particle size of the formulation was viewed and photographed using scanning electron microscope (Sigma, Carl Zeiss). The particles were coated by platinum by using vacuum evaporator and thus, the coated sample were viewed and photographed in JEOL, JSM-6701F Field emission SEM [17].

Fourier transform infrared (FTIR) analysis

By using an FTIR spectrophotometer to obtain infrared scans of pure FA, SPC-3, PM and FA-D GTE, the molecular interactions between the formulation's constituent parts were analysed (Model: FTIR-8300, Shimadzu Corporation Kyoto, Japan). To make round translucent discs individual samples (2 mg) were uniformly mixed with potassium bromide (KBR) 200 mg and compressed at a pressure of 10 ton/nm2. In order to potentially eliminate any potential influence from residual moisture, the samples were first dried in a hot air oven at 50 °C for 2 h. Each analysis consisted of 45 images with a 4 cm^{-1} resolution. The instrument's IR solution FTIR control software (version: 1.10) was used to evaluate the data [18].

Powder X-ray diffraction (P-XRD) analysis

The sample of pure FA, Phospholipids SPC-3, PM and FA-D GTE were analyzed for their polymorphic state by obtaining their X-ray diffraction scans. This was done using a powder X-ray diffractometer (Model: D8 ADVANCE, Bruker AXS, Inc. Madison, WI USA) operating with a brag-Brentano geometry (θ/20) optical setup. Briefly, the sample were mounted uniformly as a thin layer on the sample holder. A one-dimensional detector (LYNXEYE™) for X-ray diffraction based on Bruker AXS compound silicon strip technology was used to monitor diffraction. The samples were irradiated with a monochromatic CuKβ radiation (λ = 1.5406 A) By obtaining their X-ray diffraction scans, the sample of pure FA, Phospholipids SPC-3, PM, and FA-D GTE was examined for its polymorphism condition. This was accomplished utilizing a powder X-ray diffractometer with a bragg-Brentano geometry (20) optical setup (Model: D8 ADVANCE, Bruker AXS, Inc. Madison, WI, USA). In a nutshell, the samples were evenly put in a thin layer on the sample holder. Diffraction was seen using a one-dimensional X-ray diffraction detector (LYNXEYETM) based on Bruker AXS compound silicon strip technology. A monochromatic CuK radiation was used to irradiate the samples (1.5406 A°). An operating voltage and amperage of 30 mV and 10mA, respectively. The samples were scanned with the diffraction angle increasing from 3° to 60°, 2θ angle with a step angle of 0.04° 2θ and a count time of 5 second. The angular spin for the sample was 360° [19].

Functional characterization

In vitro dissolution study

A dissolution method employed to evaluate the release performance of free FA-LC and improved FA-D-GTE formulations were examined. A sealed dialysis bag was filled with aliquots of free FA and FA-phytosomes each of which was equal to 2 mg of free FA. The dialysis

bags were placed in a 180 ml release medium containing 0.25 % (w/v) Tween 80 to simulate sink conditions, phosphate-buffer saline (PBS), pH 7.4 were then incubated in a shaking water bath at 37 °C and 75 rpm. At various time intervals (1, 2, 3, 4, 6, and 12 h) release medium samples (3 ml) were taken out and replaced with the same volume of brand-new release medium. The samples were filtered using a 0.45 Millipore filter before being analyzed spectrophotometrically with a fresh release media as a blank at a max of 269 nm [20].

Ex-vivo permeation study

In the ex-vivo permeation study of the FA-PSN performed using Franz diffusion cells with goat nasal mucosa, other process parameters were the same as used for *in vitro* drug release study [21].

RESULTS AND DISCUSSION

Preparation of functionalized phytosomal soft nanoparticles

In this study, GTE and FA were used to prepare the conjugation of GTE with FA. Then the FA and GTE were precisely measured at 50 mg and 200 mg, respectively. Then dissolved in 10 ml of DMF. A little amount of methane sulfonic acid (0.1 ml) was added to the resulting solution. After boiling the prepared solution combination in a water bath for 24 h at 60 °C, the dry residue was combined with cold water to create the product's precipitation. The substance was dried at room temperature after being filtered using Whatman filter paper. The required amounts of ethanol, LIPOID®SPC-3, and conjugation were weighed precisely (30 ml) In order to make a clear solution, (100 mg) of conjugation was added to ethanol in an RBF after (200 mg) LIPOID®SPC-3 was added using a sonicator. The clear solution was then stored for two hours at 50 °C for synthesis using a condenser assembly. The solution was put into a china dish after two hours and maintained in a water bath that was heating to help the liquid evaporate. Following the addition of N-hexane, the mixture was allowed to dry before being utilised to collect the powder in a valve. The creation of phytosomal soft nanoparticles via nanoprecipitation specifically, 15 ml of dichloromethane were mixed with 100 mg of FA complex using a magnetic stirrer to generate a clear solution. This transparent solution was then put dropwise (0.2 ml/min) into distilled water while magnetic stirring was present (40 ml). FA-PSNP and a suspension of FA phospholipid with a light yellowish opalescence were created when the dispersion phase progressively evaporated while being agitated. After adding 5 % sucrose w/w in solution as a stabiliser the resultant suspension was then freeze-dried using a lyophilizer [22, 23].

Particle size and zeta potential

Particle size and zeta potential are valuable predictors of the effective distribution and physical stability of nanoparticle in a liquid medium. The ferulic acid-phospholipids complex (FA-LC) played a major role in the release as well as enhancing absorption efficiency of the FALC-PSN system shows, with lower average particle size, are known to exhibit enhanced bioavailability in the nasal administration; the particle size distribution of the optimized FALC and FALC-MS formulation. The particle size for the fig. 1-2 FALC found as 4669±0.73 and zeta potential found as 5.03 with refractive index of 1.3326±0.01, Particle size for the fig. 3-4 FALC-PSN was found as 3.08±0.01. Zeta potential were-12.15 with polydispersity index of 0.01±0.02, respectively. Zeta potential (ζ), a measure of the surface charge on the particle, is indicative of the physical stability of the formulation in a complex and complex-microsphere system [24].

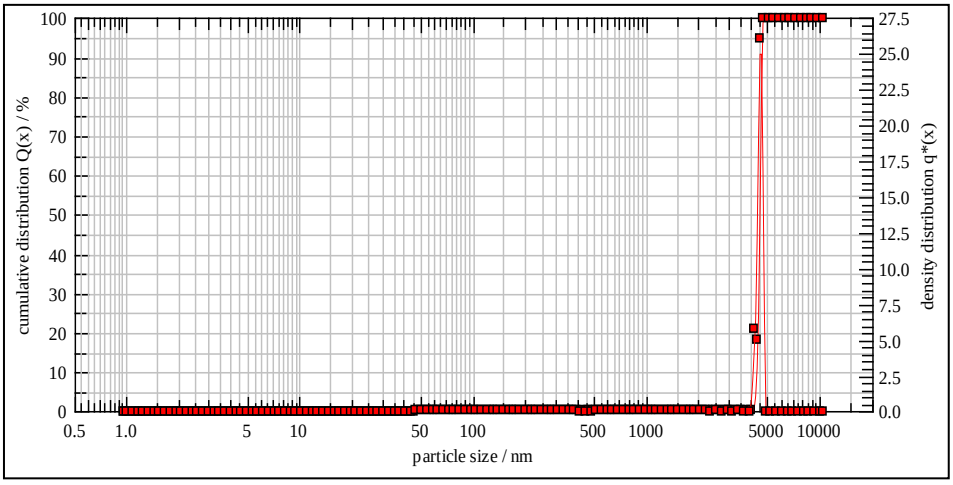


Fig. 1: Particle size of FALC

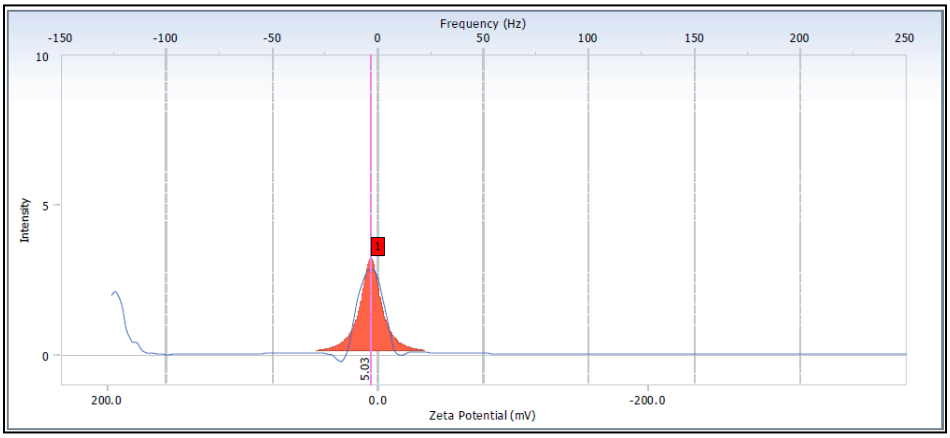


Fig. 2: Graph of zeta potential of FALC

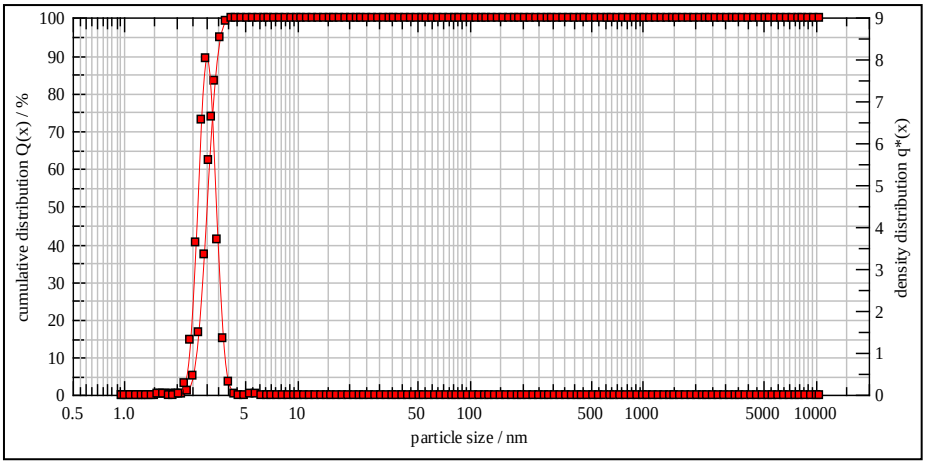


Fig. 3: Graph of particle size of prepared FALC-PSN

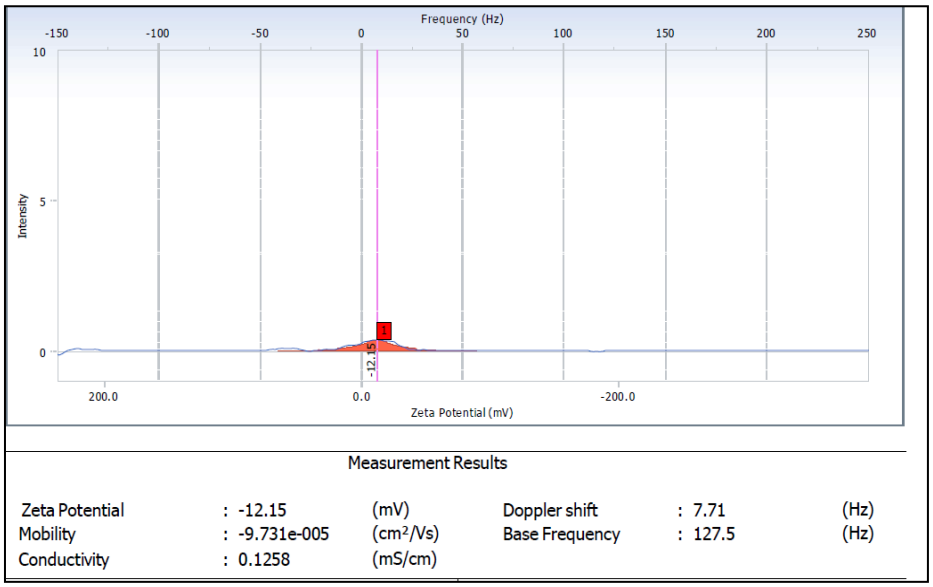


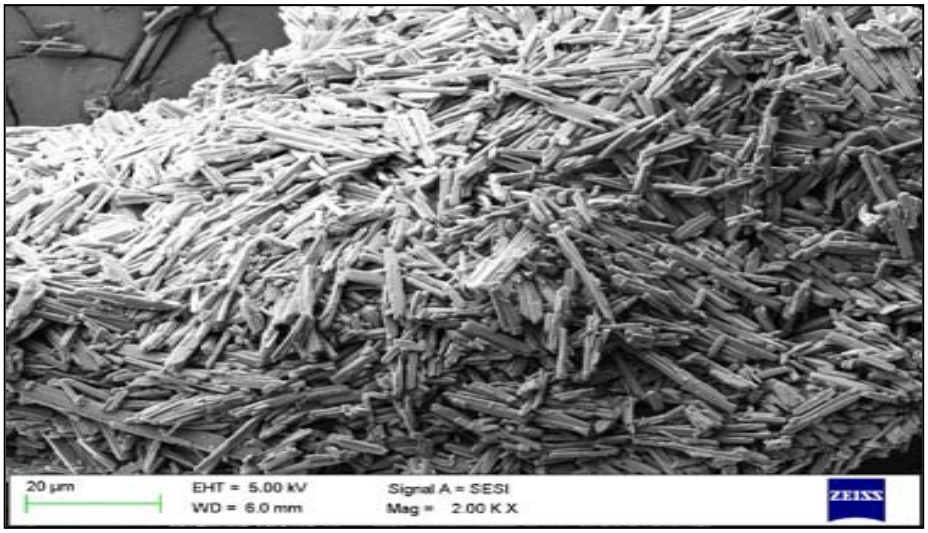
Fig. 4: Graph of zeta potential of FALC-PSN

Scanning electron microscopy (SEM) analysis

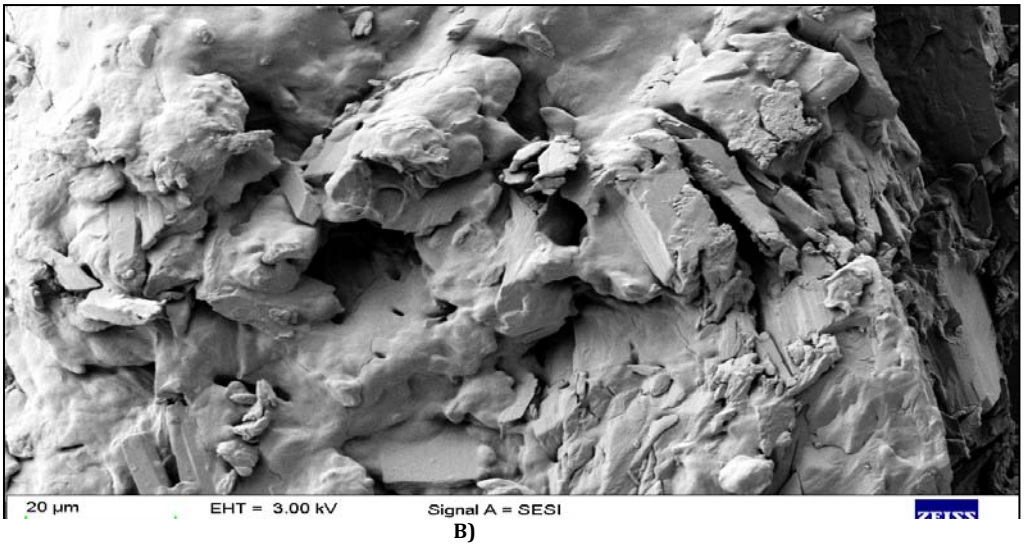
The surface morphology of FA-D GTE complex and FA-LC PSN was examined by SEM and illustrated. The complex was made up of GTE and appeared as amorphous particles. A scanning electron photomicrograph of an optimized drug-loaded Phospholipid Nanoparticle was taken. A small amount of nanoparticles was spread on glass stub. Afterwards, the stub containing the sample was placed in the scanning electron microscope chamber. The scanning electron photomicrograph was taken at the acceleration voltage of 15 kV, chamber pressure of 4.58e-6 torr, and magnification 1200 [25].

Fourier transform infrared (FTIR) analysis

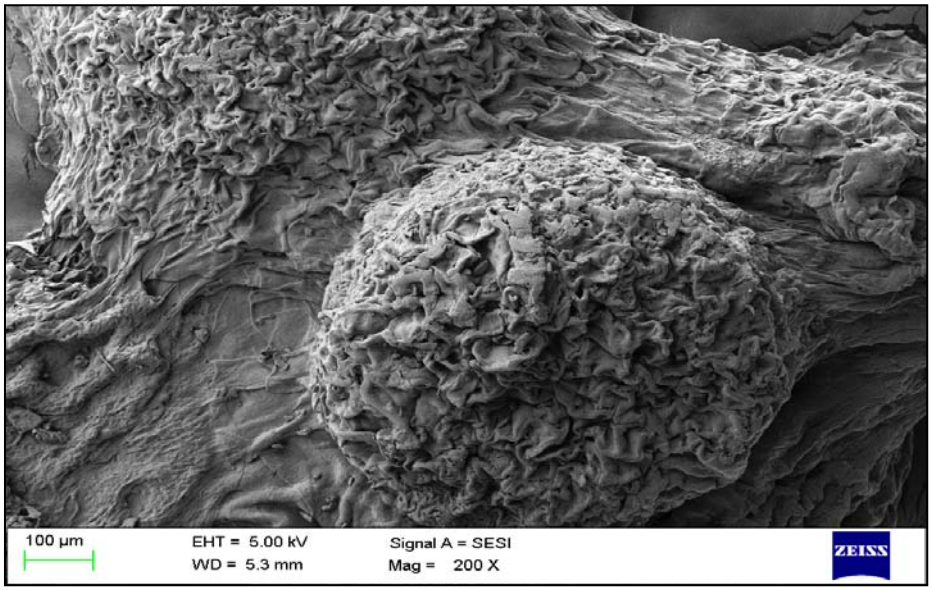
The FTIR spectrum of FA various polymers and their combination was recorded at room temperature on FTIR (Agilent Technologies Cary 630 FTIR) in data region 4000 cm^{-1}. The sample or physical mixture of drug and polymer is placed on platform. The FTIR spectra of pure drug ferulic acid were found to be similar to the standard spectra of the drug. It was observed that FTIR analysis of drug alone and with blend of various polymers are compatible with each other. The polymers used do not show any type of chemical or structural changes in the drug. FTIR spectra were analysed. As earlier reported [37], characteristic peak of native FA (fig. A) were observed at 3438.6 cm^{-1} (-OH stretching) 1431.3 cm^{-1}, and 14648.1 cm^{-1} showed (C=C aromatic ring). The FTIR spectra of lipoid®SPC-3 showed characteristic peak at 2847.7 cm^{-1} and 2914.8 cm^{-1} (CH2 stretching) at the peak level of 1733.2 cm^{-1} showed (C=O stretching) and the peak level of 1468.6 and 1375.4 cm^{-1} observed as (PO2 stretching). In (fig. C) we observed FTIR spectra of FA with GTE showed characteristic peak at 3205.5 cm^{-1} and 2940.9 cm^{-1} showed (–COOH), character peak 3384.4 cm^{-1} showed alcohol 1297.1 cm^{-1} showed alkyl ketone 1366.8 cm^{-1} showed (C-O) and 1043.7,1151.7 cm^{-1} and 1103.3 cm^{-1} showed alkylamine group. The FTIR spectra of FA with GTE showed characteristic peak at 3429.2 cm^{-1} Alcohol(O-H), at peak level 2967.0 cm^{-1} showed (-COOH), 1658.7 cm^{-1} and1688.5 cm^{-1} peak shows Alkene and (C=C aromatic ring), at peak level 1200.2 cm^{-1} and 1155.5 cm^{-1} showed alkylamines groups and 1263.6 cm^{-1} showed alkyl ketone. The FTIR spectra of D-GTE with LIPOID® SPC3, showed characteristic peak at 1237 cm^{-1} shows alkyl ketone group, 2351 cm^{-1} peak shows (COOH) group and1733.2 cm^{-1} shows ketone group and 1054.8,1088 shows the alkyaline group. The FTIR spectra of D-GTE with LIPOID® SPC3, showed characteristic peak at 2975.0, 2805 and 3015.4 shows (-COOH), 2117.7 shows (C=C stretching), 1826.4 and 1688.5 shows the aromatic ring and 1162.9,1257.3 and 1323.2 shows the alkyl ketone [26].



A)

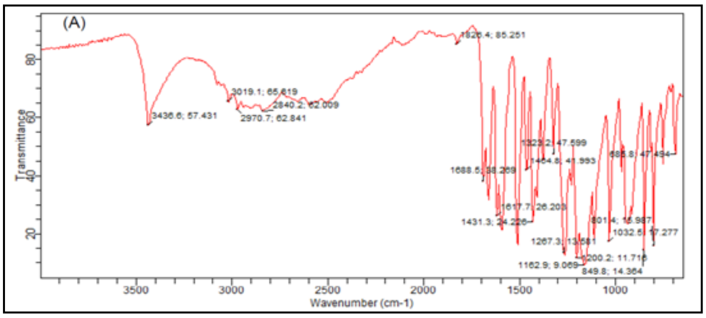


B)

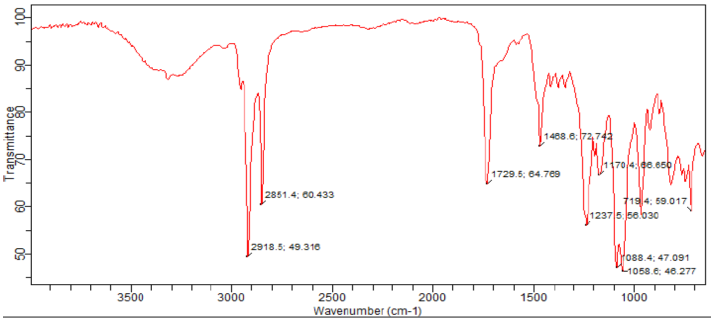


C)

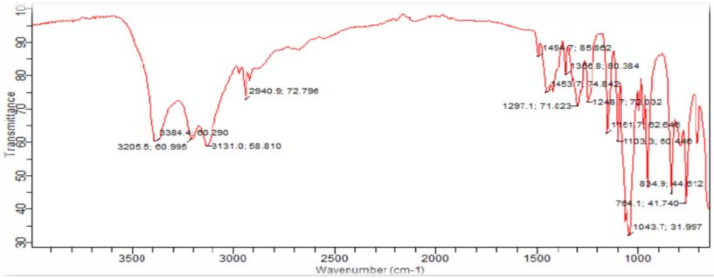
Fig. 5: SEM of A) FA B) FALC C) FALC-PSN


(A)
Transmittance
Wavenumber (cm-1)
3436.6; 57.431
3019.1; 65.619
2970.7; 62.841
2840.2; 62.009
1825.4; 85.251
1688.5; 38.269
1617.7; 26.203
1431.3; 24.226
1323.2; 47.599
1464.8; 41.993
1267.3; 13.561
1162.9; 9.069
1200.2; 11.716
849.8; 14.364
801.4; 18.987
1032.5; 17.277
685.8; 47.494

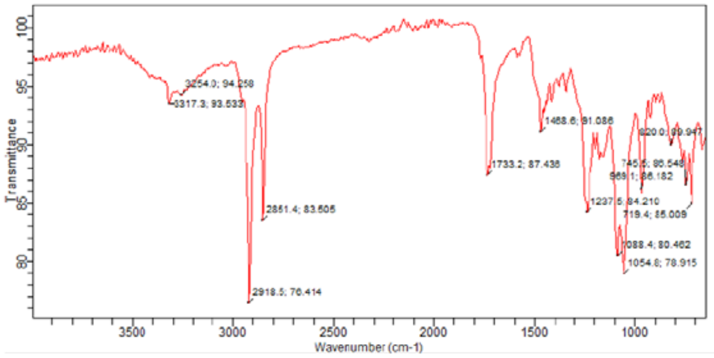
A)


Transmittance
Wavenumber (cm-1)
2918.5; 49.316
2851.4; 60.433
1729.5; 64.769
1468.6; 72.742
1170.4; 66.650
1237.5; 56.030
719.4; 59.017
1088.4; 47.091
1058.6; 46.277

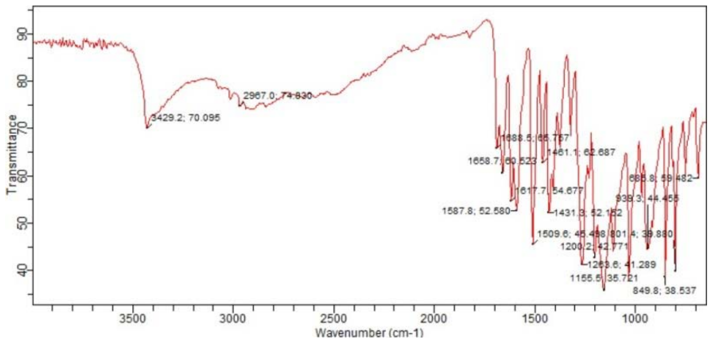
B)


Transmittance
Wavenumber (cm-1)
3205.5; 60.995
3384.4; 60.290
3131.0; 58.810
2940.9; 72.796
1494.7; 85.862
1386.8; 80.384
1453.7; 74.842
1297.1; 71.023
1248.7; 72.032
1151.7; 62.646
1103.3; 60.446
834.9; 44.512
764.1; 41.740
1043.7; 31.997

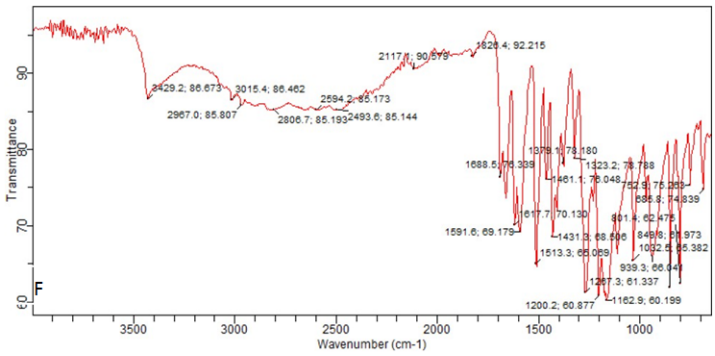
C)


Transmittance
Wavenumber (cm-1)
3254.0; 94.258
3317.3; 93.533
2851.4; 83.605
2918.5; 76.414
1733.2; 87.436
1468.6; 91.086
1237.5; 84.210
820.0; 89.947
745.5; 86.548
969.1; 86.182
719.4; 85.009
1088.4; 80.462
1054.8; 78.915

D)

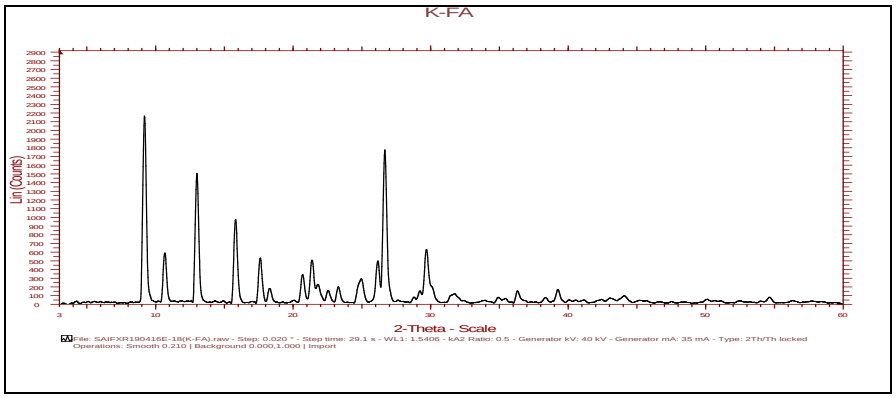

Transmittance
Wavenumber (cm-1)
3429.2; 70.095
2967.0; 74.830
1688.5; 65.757
1658.7; 60.523
1461.1; 62.687
1617.7; 54.677
1587.8; 52.580
1431.3; 52.152
1509.6; 45.458
1200.2; 42.771
801.4; 39.880
1263.6; 41.289
1155.5; 35.721
685.8; 59.482
938.3; 44.455
849.8; 38.537

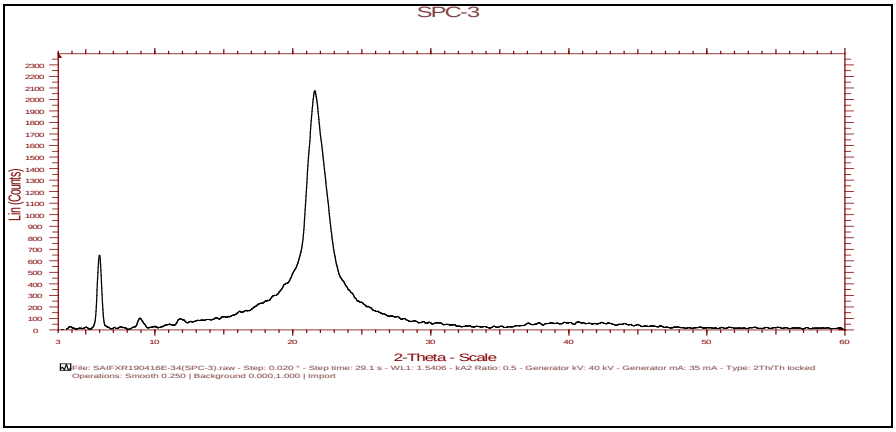
E)

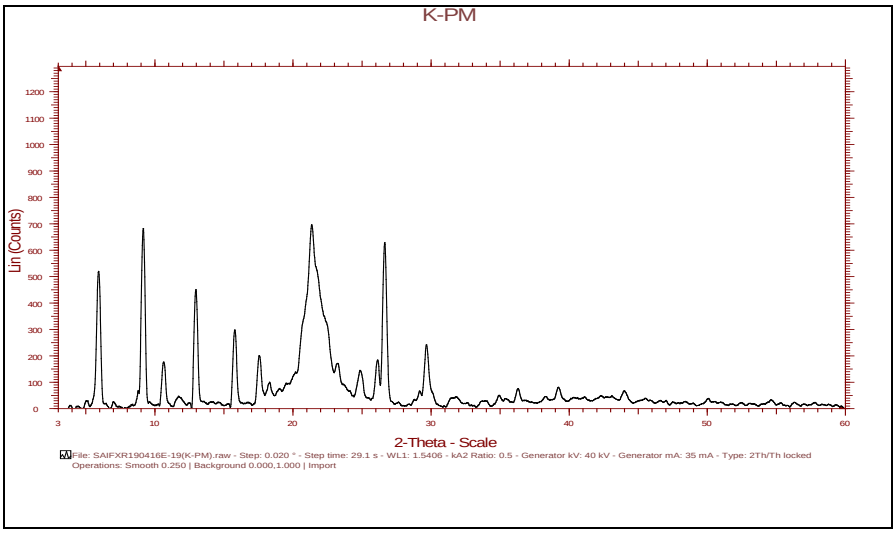


F)

Fig. 6: FTIR of A) FA B) LIPOID®SPC-3 C) D-GTE D) FA with D-GTE E) D-GTE with LIPOID®SPC-3 F) FALC-PSN







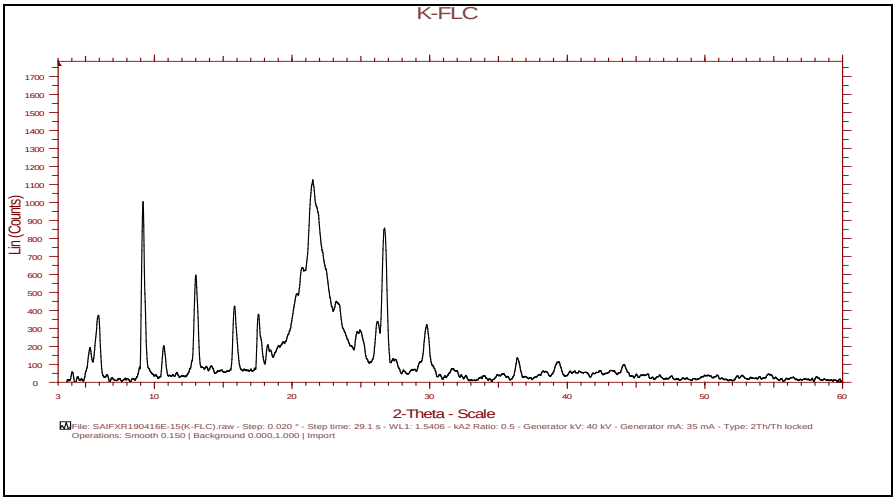


Fig. 7: Diffractogram of A) FA B) lipoid SPC 3 C) physical mixture D) FALC-PSN

Powder X-ray diffraction (P-XRD) analysis

The X-ray diffractograms of pure FA, pure Phospholipids SPC 3, and FA-D GTE are shown in the Fig: (A, B, respectively). The diffraction pattern of pure FA (fig. A) displayed intense and sharp crystalline peak at 2θ=9°, 10°, 11°, 13°, 20°, 26°, 28° and 29° characteristic of crystalline nature of FA. The phospholipids SPC-3 (fig. B) exhibited a single relatively broad peak at around 2θ=20°. Absences of other peak indicate the amorphous nature of the SPC-3. As previously reported [38]. The FA phytoconstituent from the category of flavonoids along with the FA were selected for the formulation of the (FA-D GTE) i.e. phytosomes; the selected FA and GTE were evaluated for the preformulation study i.e. solubility, melting point, Sample were shown good melting point results with having good solubility in ethanol, nearly positive. The FA-D GTE along with the-SPC3 (hydrogenated soya phosphatidylcholine) were selected for the formulation of the FA-PLC i.e. phytosomes the selected FA and phospholipids were evaluated for the preformulation study i.e. Solubility, melting point, and other chemical tests as well. Sample were shown good melting point results with having good solubility in ethanol and slightly soluble in water, a nearly positive test for all chemical tests. The prepared FA-D GTE was formulated by the solvent evaporation method, using ratios of the FA and GTE. The ratio of the prepared complex system was based on the previous literature reviews. Those who successfully evaluate and extent the drug delivery of FA in liver cancer. The ratio of the complexes was taken as (1:1) the complex was prepared. Which may be a novel drug delivery system for liver-targeting diseases [27, 28].

Functional characterization

***In vitro* dissolution study**

The result of the comparison of the dissolution profile of pure FA with FA-GTE and phosphate buffer solution (pH 7.4). The release profile of the FA was extended to 35.37 % in 12 h. In contrast, the release of FA form FA D-GTE LC continued to increase, reaching 78.39 % after 12 h. The difference in the release rate of FA from the two formulations can be attributed to the increased solubility the prepared phytosomes. Pure drug has low aqueous solubility, which is shown to be improved by the amphiphilic nature of the SPC-3, FA is assumed to change from the crystalline state to the partially amorphous state in the FA-D GTE-LC, which may extend the rate and extend of dissolution to 12 h. and the change in the structural morphology of the FA due to the nature of LIPOID®SPC-3 allow for greater wetting of FA-D GTE and improved dispersion [29].

Percent drug diffusion study by using goat nasal mucosa. An *Ex-vivo* drug diffusion study of the microspheres was performed using a Franz-diffusion cell with the goat nasal mucus membrane, in which the donor compartment contained the microspheres while the receptor compartment was filled with the phosphate buffer solution of pH 6.6 that was within the pH range in the nasal cavity.

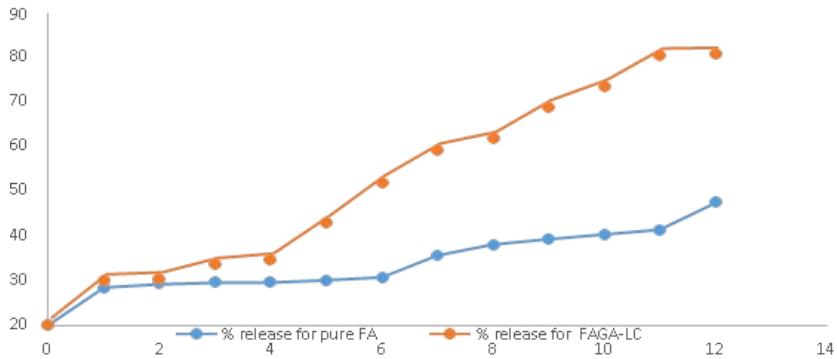


Fig. 8: The *in vitro* dissolution profile of FA and FALC-LC *Ex-vivo* permeation study, *Each value represents mean, (n=3)

The performed *in vitro* drug diffusion profile of FA, FAC-PSNP and FALC-PSNP showed the characteristic increase in the diffusion profile, respectively. As a result, the FA has drug diffusion in goat nasal mucosa at 58.22 %, the FA-C-PSN has showed 72.94 % and the FALC-PSN showed characteristic hike in the drug diffusion at 80.04% and has higher drug diffusion than both formulations, which indicate that the drug had increases its aqueous solubility and also change with the structural morphology. All the focus were take place at the drug release exponent values are estimated to be higher than FA and FAC-PSN formulation. Thus the FALC-PSN has significantly enhance both of the rate and the extent of FA permeation in the goat nasal mucosa through the Franz-diffusion apparatus [30, 31].

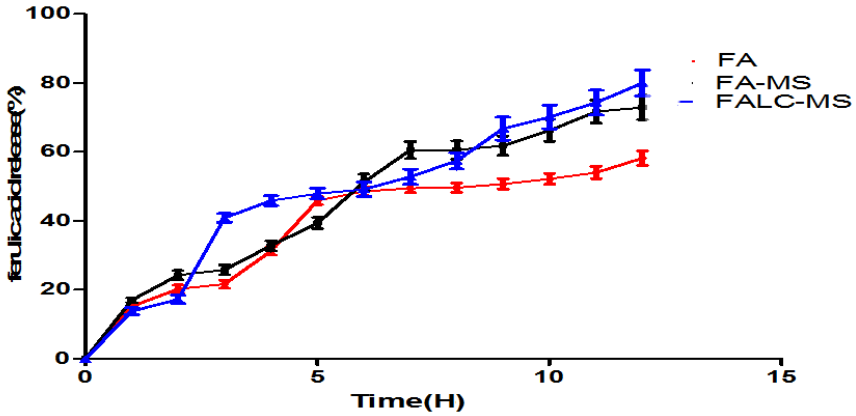


Fig. 9: *Ex-vivo* permeation profile of FA, FAC-PSN and FALC-PSN, *Each value represents mean±SD, (n=3)

CONCLUSION

Hence from the present experimental data, it was concluded that the proposed project was achieved. In this study, all the literature survey and study about the GTE, SPC-3 and FA were confirmed to decide the value of GTE-FA-SPC-3 ratio for the preparation of the complex. Reaction temperature, time and volume of solvent were significantly influence the dependent variable of drug content (% w/w). The particle size, zeta potential and SEM of final formulation are awaited. The FTIR and P-XRD of the phospholipids complex showed formed with bonds such as hydrogen bond and Van-derwaals force. The batch of complex showed extended release of FA than pure FA suspension. The prepared liver targeting delivery system of FAGA-LC-NP had shown the good promising results for all the evaluated parameters. And the *In vitro* dissolution parameter showed the result of the prepared formulation ferulic acid D-galactose lipid complex phytosomal soft nanoparticles (FA-D GTE-LC-PSN) show the 78.39 % drug release at 12 h and pure FA shows was extend to the 35.37 % in 12 h in contrast. The difference in the release rate of FA from the two formulations can be attributed to the increased solubility and increased wet ability in the prepared phytosomes. Pure drug has low aqueous solubility, which is shown to be improved by the amphiphilic nature of the SPC-3. The *Ex-vivo* permeation was studied.

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AUTHORS CONTRIBUTIONS

All the authors contributed equally.

CONFLICT OF INTERESTS

There is no conflict of interest among authors.

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