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"Development and characterization of novel matrix dispersion system based on phospholipid complex for improving oral delivery of ferulic acid"

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Abstract

Phospholipid complex is one of the most successful approaches for enhancing oral bioavailability of poorly absorbed plant constituents. But the sticky property of phospholipids results in an unsatisfactory dissolution of drugs. In this study, a matrix dispersion of ferulic acid based on phospholipid complex (MD-FAPLC) was prepared by a sonocomplex method, in which pentaerythritol was employed for improving the dispersibility of ferulic acid phospholipid complex (FAPLC) and increasing dissolution of ferulic acid. The combination ratio of ferulic acid, phospholipid and pentaerythritol was 1:2:5. The pentaerthritol use as dissolution enhancer and dispersing agent. Differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM) and Fourier Transform Infrared (FTIR) analyzes demonstrated that ferulic acid was fully transformed to an amorphous state in MD-FAPC and phospholipid complex formed. The water-solubility and n-octanol solubility of ferulic acid in MD-FAPC significantly increased compared with those of pure FA. Compared with FA and FAPC, the cumulative dissolution of MD-FAPLC at 120 min. the dissolution of MD-FAPC increase compare to pure FA. The novel MD-FAPLC significantly enhanced the oral bioavailability of ferulic acid by improving the dissolution and permeability of ferulic acid without destroying the complexation state of ferulic acid and phospholipids.

Keywords: Ferulic acid**,** LIPOID® S 100, pentaerythritol. Phospholipid complex

Introduction

Almost 90% of drug are orally administered. Absorption of drug, bioavailability pharmacokinetics profile, of orally administered drug is highly depending on the solubility of the compound in aqueous media. The oral administration of drugs is the most common route because of its good patient compliance and the lower cost

of manufacturing compared with other routes. However, low bioavailability is a major challenge for the oral dosage form development. The poor bioavailability of drugs is mainly attributed to the poor aqueous/lipid solubility and low plasma membrane permeability . Among the numerous approaches explored in recent years for the improvement of oral bioavailability of poorly absorbed drugs, phospholipid complex has received increasing attention and become one of the most successful methods. Phospholipid complex exhibits the significant capability to increase the water solubility of drugs and also promote the permeation across the intestinal epithelium in most studies. However, due to the sticky nature of phospholipids, phospholipid complex tends to aggregate and agglomerate. This disadvantage results in an unsatisfactory dissolution and oral absorption of drugs, although phospholipid complex could increase the dissolution of drugs to a certain extent compared with free drugs. Therefore, it is necessary to choose suitable carriers to disperse phospholipid complex and thereby to increase the dissolution of drug.

Phospholipids

Phospholipid also known as phosphatides, are class of lipid whose molecule has a hydrophilic head containing a phosphate group and two hydrophobic tails derive from fatty acid join by a glycerol molecule. The phosphate group can be modified with simple organic molecule such as choline, ethanol or serine. Phospholipid are key component of cell membrane. The first phospholipid identify in 1847 as such in biological tissue was lecithin, or phosphatidylcholine in the egg yolk of chickens by the French chemist and pharmacist Theodore Nicolas Gobley.

Lipid-based drug delivery systems

Lipid based drug delivery systems (LDDS) consists of a diverse group of formulations, each consisting of varying functional and structural properties that are amenable to modifications achieved by varying the composition of lipid excipients and other additives. Generally, most lipid drug delivery systems used as drug carriers have high stability, high carrier capacity, feasible for incorporating into both hydrophilic and hydrophobic substances and variable routes of administration, including oral, topical, parenteral and pulmonary routes .Lipids have gained much interest as carriers for the delivery of drugs with poor water solubility .The availability of novel lipid excipients with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid based formulations as a means for drug delivery. Lipid-based formulations can be applied to influence the absorption of active ingredients through different mechanisms, such as modifying the release of active ingredients, improving their bioavailability and stability, changing the composition and character of the intestinal environment, stimulating the lymphatic transport of active ingredients, and interact with enterocyte-based transport processes and reducing unwanted drug side effects

Structure of phospholipid

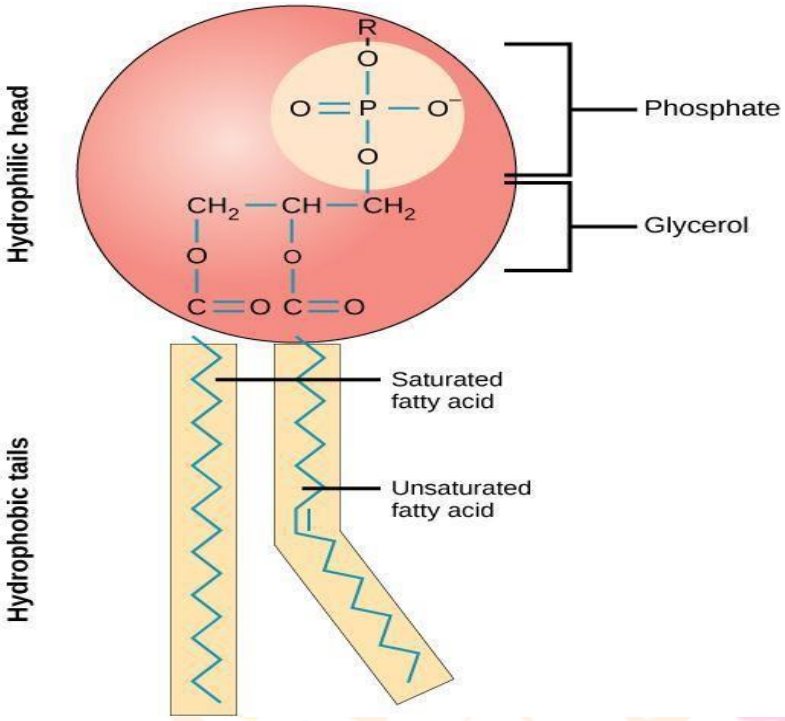


Fig. 1. Phospholipid molecule with two fatty acids and a modified phosphate group attached to a glycerol backbone.

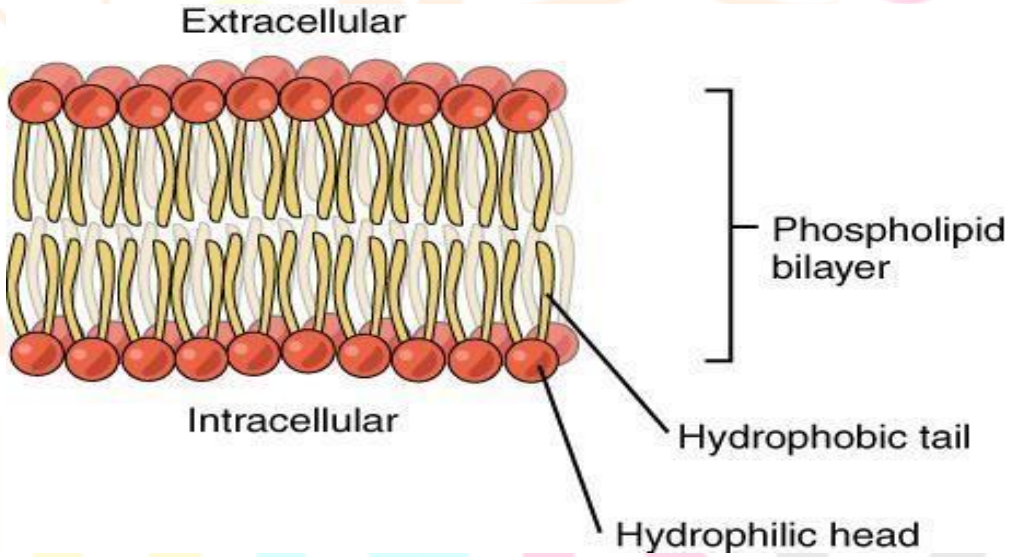


Fig. 2. Basic elements of a lipid, with the arrangement into the lipid bilayer structure

A hydrophilic head. The hydrophilic head contains the negatively charged phosphate group, and may contain other polar groups. The hydrophobic tail usually consists of long fatty acid hydrocarbon chains. When placed in water, they form various structures depending on their specific properties. Mostly, they form micelles or are organized as lipid bilayers with the hydrophobic tails lined up against one another and the hydrophilic head-group facing the water on both sides. Glycerol containing phospholipids are most commonly used component of liposome formulation and represent more than 50 % of weight of lipid in biological membranes. These are derived from phosphatidic acid. The back bone of the molecule is the phosphoric ester of glycerol . One of the

OH groups of phosphoric acid may be further esterified to a wide range of organic alcohols including glycerol, choline, ethanolamine, serine and inositol. Examples of phospholipids are phosphatidylcholine (PC), phosphatidyl ethanolamine (PE), phosphatidyl serine (PS), phosphatidyl inositol (PI), and phosphatidyl glycerol (PG) for stable liposomes, saturated fatly acids are used. Unsaturated fatty acids are not used generally

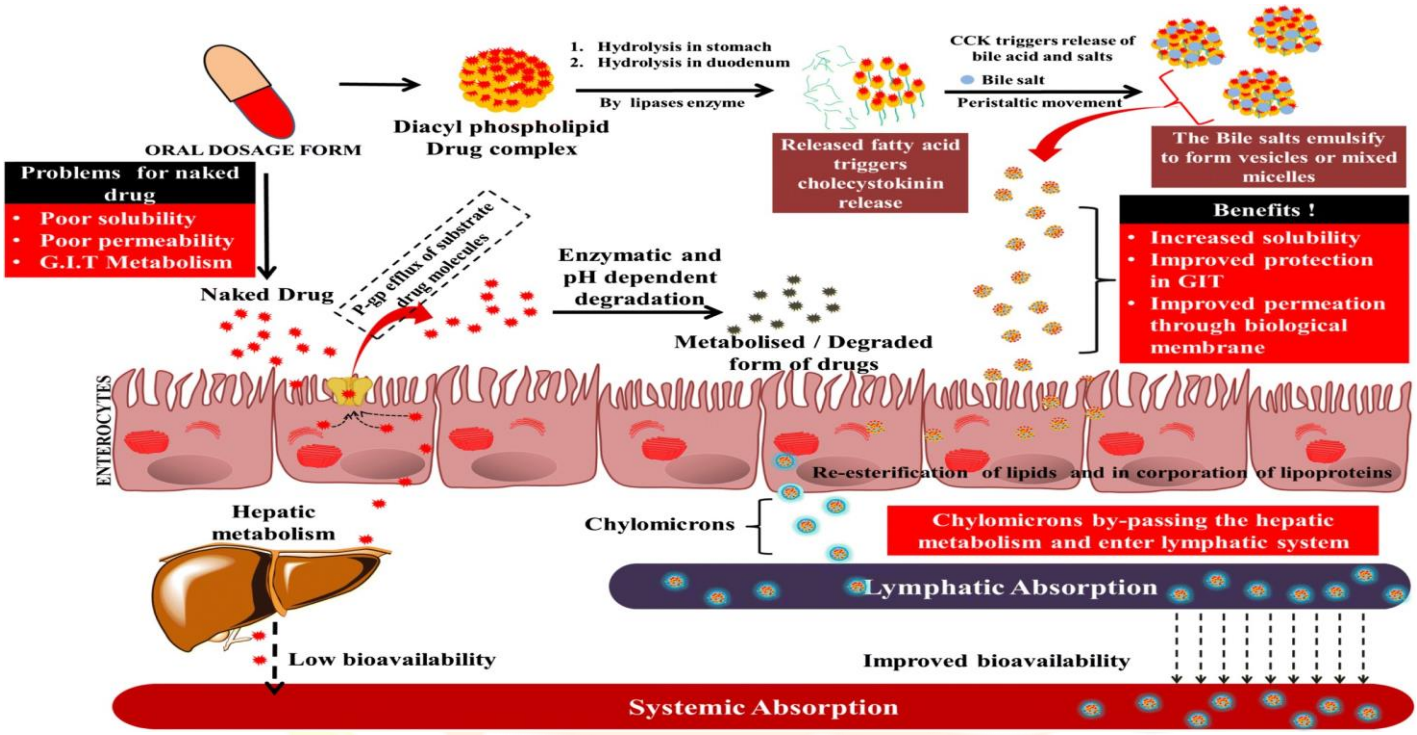


Fig 3. The general mechanism of drug phospholipid complex to enhance bioavailability

Material and methods

Materials:

Table No.3 Lists of Materials

Sr. No.	Name of Ingredients	Name of Supplier
1	Ferulic acid	Yucca Enterprises, Mumbai
2	Disodium hydrogen phosphate	Ozone International , Ahmedabad
3	Ethanol	C S corporation
4	LIPOID® S 100	Lipoid
5	n- Hexane	Ozone International, Ahmedabad
6	n- Octanol	Ozone International, Ahmedabad
7	Pentaerythritol	Ozone International, Ahmedabad
8	phosphate Potassium dihydrogen	Ozone International, Ahmedabad

Equipment:

Table No. 4 List of Equipments

Sr.No.	Equipment	Model & Make
1	Dissolution apparatus	TDT 08L
2	Differential scanning colorimetry	Supra®, Carl Zeiss NTS Ltd., Germany
3	FT-IR spectrophotometer	FT-IR-8300, Shimadzu, Kyoto, Japan
5	Maganetic stirrer	V.S Akola
6	Sonicater	Ambala V.S Akola
7	Scanning electronic microscope	Supra®, Carl Zeiss NTS Ltd., Germany
8	x- ray diffractometer	D8 ADVANCE, Bruker AXS, Inc., Madison, WI, USA
9.	Zeta potential	Nanophox Sympatec, GmbH, Clausthal-Zellerfeld, Germany

Methods

1. **Preparation of ferulic acid phospholipid complex (FAPLC)**

Ferulic acid phospholipid complex (FAPLC) was prepared at a ferulic acid: phospholipid ratio of 1:2 (w/w) by a sonocomplex method. Briefly, the ferulic acid (20 mg) and phospholipid (LIPOID® S 100) (194mg) were accurately weighted in 100ml round bottom flask dissolved in ethanol (20ml) at room temperature. The mixture was sonication for 2 hr. After the sonication the ethanol evaporated with help water bath 1-2 ml liquid residue was resulting add 10ml of n- hexane in formation of FAPLC. The obtained FAPLC was dried at 40 °C under vaccum for 12 hr. dried FAPLC was stored in amber color glass vial and analysis further.

2. **Preparation of matrix dispersion ferulic acid phospholipid complex (MD-FAPLC)**

The matrix dispersion ferulic acid phospholipid complex was prepared at ferulic acid: Phospholipid: pentaerythritol ratio of 1:2:5 by sonocomplex method Briefly, the feulic acid (100mg), phospholipid (200mg) and pentaerythritol (500mg) were accurately weighted in round bottom flask dissolved in ethanol (20ml) at room temperature. The mixture sonication for 2 hr. After the sonication the ethanol evaporate with help water bath 1-2 ml mixture aside ethanol completely evaporate at room temperature in formation of MD-FAPLC. The obtained MD-FAPLC was dried at 40 °C under vacuum for 12 hr. dried FAPLC was stored in amber color glass vial and analysis further.

3. **Physical-chemical characterization of MD-FAPLC**

I. **Particle size and zeta potential**

Particle size and zeta potential are the most widely used indicator for the determination of release behavior and physical stability of a multi particulate system dispersed in the liquid medium. In this study, the particle size and size distribution of ferulic acid (FA) within MD- FAPLC were evaluated using Photon Cross-Correlation Spectroscopy (PCCS) equipped with Dynamic Light Scattering (DLS) technology Briefly, the matrix dispersion of FAPLC was analyzed for particle size within the sensitivity range of 1 nm to 10 µm using

a particle size analyzer (Model of zeta potential within the sensitivity range of – 20: Nanophox Sympatec, GmbH, Clausthal-Zellerfeld, Germany). The same dispersion of formulation was also used for the analysis 0 to +200 mV using Nano Particle Analyzer (Model: NanoPlusTM-2, Particulate System, and Norcross, GA, USA) .

II. Scanning electron microscopy (SEM)

The samples of FA, PM, LIPOID® S 100, Pentaerythritol, and MD-FAPLC were analyzed to study their surface characterization using a scanning electron microscope (Model: Supra®, Carl Zeiss NTS Ltd., Germany. Briefly, the samples (~50 mg) were weighed and spread as a thin layer on double-faced carbon tape and then loaded into the sample chamber of the SEM. After loading, the sample was coated using gold (~400°) via a sputter coating technique. The coated sample was scanned at an accelerating voltage of 10 kV. The scanned image of each sample a various magnifications was analyzed using instrument attached software (Smart®SEM V05.06) .

III. Differential scanning calorimetry (DSC)

The FA, PM, LIPOID® S 100, Pentaerythritol, and MD-FAPLC were analyzed to investigate their thermal properties using differential scanning calorimeter (Model: DSC-1821e, MettlerToledo AG, Analytical, Schwerzenbach, Switzerland). Briefly, the sample (~2mg) was weighed and loaded into a previously calibrated and N2 purged analyzing area. The loaded sample was subjected to heating at a rate of 10 °C/min in the heating range of 0 to 400 °C. Following heating, the generated DSC thermograms of each sample were read using instrument attached software (Universal Analysis 2000, V4.5A, Build 4.5.0.5).

IV. Fourier transforms infrared spectroscopy (FT-IR)

FT-IR is a valuable analytical tool often used in the identification of functional group interaction between the formulation components. The FA, PM, LIPOID® S 100, pentaerythritol and MD-FAPLC were analyzed using the FT-IR spectrophotometer (Model: FT-IR-8300, Shimadzu, Kyoto, Japan). Briefly, the powder mixture of samples and FT-IR grade of potassium bromide was compressed into thin transparent discs using Mini Hand Press Machine (Model: MHP-1, P/N-200-66, 747-91, Shimadzu, Kyoto, Japan). This disc was then scanned at a wavenumber range of 400 to 4000 cm-1 under the scanning resolution of 4 cm-1. The scanned image of each FT-IR sample was analyzed and interpreted using instrument accompanied software (IR Solution, version 1.10) .

V. Powder x-ray diffractometry (PXRD)

A powder x-ray diffractometer (Model: D8 ADVANCE, Bruker AXS, Inc., Madison, WI, USA) was employed for the comparative analysis of crystal characteristics of FA, PM, LIPOID® S 100, pentaerythritol and MD-FAPLC respectively. Briefly, samples (~50 mg) were loaded into a sample analyzing area and irradiated using the CuKβ radiation source (ƛ = 1.5406A0°). The irradiated sample was scanned and detected using a dimensional silicon strip based technology detector (LYNXEYE™). The obtained diffraction spectra on the 2θ angle between the ranges of 3 to 60° at a count rate of 5 s were interpreted using PXRD accompanied software. An earlier published procedure by our group has been followed for the PXRD analysis of samples .

VI. Solubility studies

A method for the solubility analysis of pure FA, PM, MD-FAPLC respectively. Briefly, the above-mentioned samples in an excess quantity were dispersed in 5 mL of distilled water or noctanol in sealed glass vials. The content in the vials was then agitated using a shaker (Model: RSB-12, Remi House, Mumbai, India) for 24 h. After agitation, the developed dispersion was centrifuged at 1500 rpm for 25 min followed by filtration using a 0.45 µ membrane filter. The filtrate was suitably diluted and analysed the solution at the maximum wavelength of (ƛmax=~311 nm) against the blank to determine the solubility of each sample in water or noctanol. The sample absorbance was recorded using an UV-visible spectrophotometer (Model: V-630, JASCO International Co., Ltd. Tokyo, Japan) .

4. Functional characterization of MD-FAPC

I. *In vitro* dissolution studies

The dissolution properties of pure FA, PM and MD-FAPLC were evaluated using USP method II (paddle method) on a dissolution tester (Model: TDT-08LX, Electrolab India Pvt. Ltd., Mumbai, India). The samples of pure FA (50 mg) ,PM (equivalent to ~50 mg FA) MD-FAPC formulation (equivalent to ~50 mg FA) was dispersed onto continuously stirred (100 RPM) dissolution media (Phosphate buffer, pH 6.8), maintained at 37 ± 0.5°C. For analysis, aliquots of samples were withdrawn at predetermined intervals and filtered (0.45 µm). The sink conditions in the dissolution vessels were maintained by replenishing with fresh medium in quantities equal to those of the withdrawn samples. The filtered analyse, after suitable dilutions, was assayed for UA absorbance at λ = 314 nm, 285 nm, 232 nm on a UV-visible spectrophotometer (Model: V-630, JASCO International Co., Ltd., Tokyo, Japan). Temporally obtained absorbance values were converted into cumulative dissolution profiles (%) for the purpose of reporting.

Result and discussion:

Preformulation studies

Identification test for FA

Table No. 5. Identification test for FA

Sr no.	Chemical Test	Observation	Inference
1	Shinoda test	Crimson green colour	Positive test
2	Alkaline reagent test	Yellow colour to colourless by addition of dilute acid	Positive test
3	Zinc chloride test	Red colour	Positive test

Identification test for LIPOID® S 100:

Table No.6. Identification test for LIPOID® S 100

Sr.no	Chemical test	Observation	Inference
1	Powder of Lipoid S100 on a glass slide +drop of Sudan red-III reagent after two minutes wash with 50% alcohol + mount in glycerine + observed under the microscope oil globule appears red.	Oil globules appears red	Positive test

Organoleptic properties

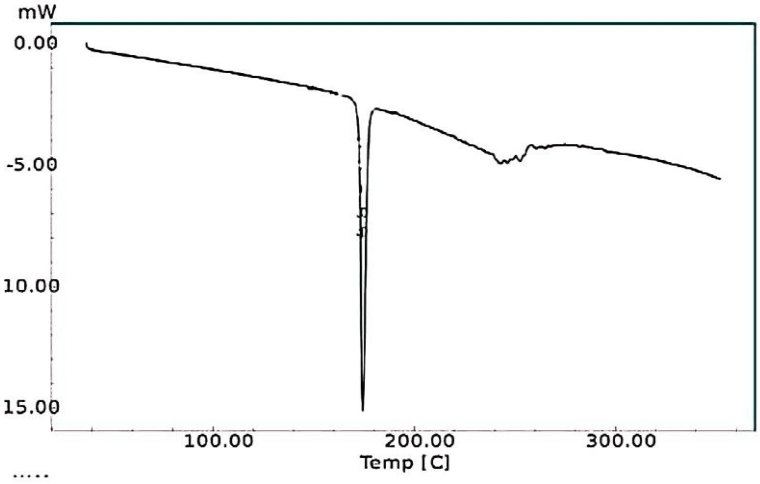
Table No.7. Organoleptic properties

Sr. no	sample	Appearance	Colour	Melting point	Solubility in water
1	Ferulic acid	Crystalline powder	white	168-172 C	0.78 g/L
2	Pentaerythritol	Crystalline powder	white	260 C	0.86 g/ L

Differential scanning calorimetry

DSC is a valuable tool particularly used to determine the physical and solid-state interaction (i.e. appearance, disappearance, shifting, and/or alter the peak position and area) between the components of formulations. The DSC curve of FA, pentaerythritol, LIPOID® S 100 PM and MD-FAPLC are shown in Fig.4 (A-E) respectively. The FA DSC curve (Fig. 4A) displayed a high-intensity endothermic peak around ~174.25 °C with an enthalpy value ~105.16 J/g indicates polymorphic form I of FA. The Pentaerythritol thermo gram showed two dissimilar endothermic peaks (Fig.4B). First broad peak appeared around ~ 196°C and is possibly due to the phase transition of pentaerythritol from its usual tetragonal form (crystal structure II) to cubic lattice structure (crystal structure I). These changes were also supported by the reported entropy of transition of ~23 Cal/degree/mole. Second small diffused endothermic peak was exhibited at ~281.5°C, indicating the melting of pentaerythritol. The LIPOID® S 100 thermogram peak show in (Fig.4C). The endothermic peak around ~109.75°C, ~239.61 °C and ~280.37 °C. Fig 4D show the DSC cure of PM. The endothermic peak around ~197.08 °C,

~269.94 °C and ~336.53 °C to show the interaction of FA, pentaerythritol and LIPOID® S 100.The DSC cure of MD-FAPLC show in Fig.4E. the endothermic peak around ~198.84 °C,~253.54 °C and ~336.82 °C show the interaction of FA, pentaerythritol and LIPOID® S 100 convert to crystalline to amorphous state.



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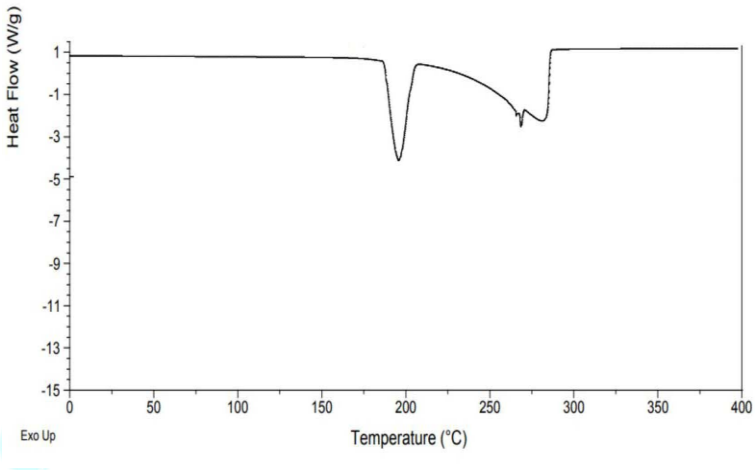

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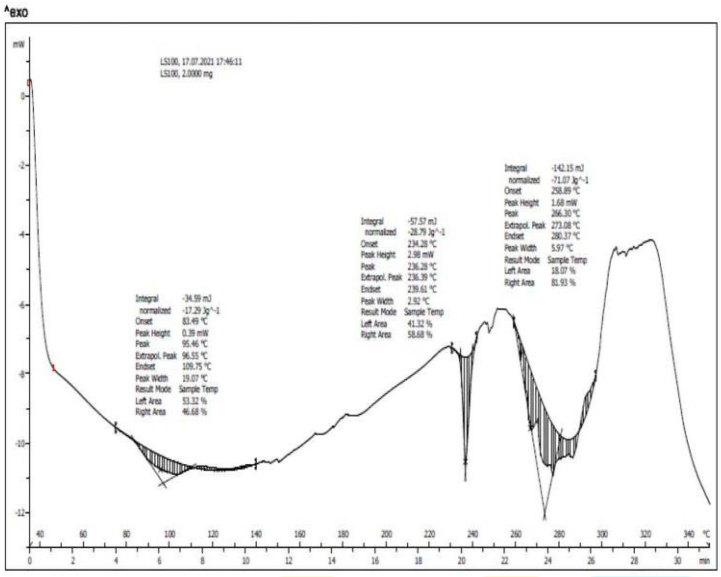

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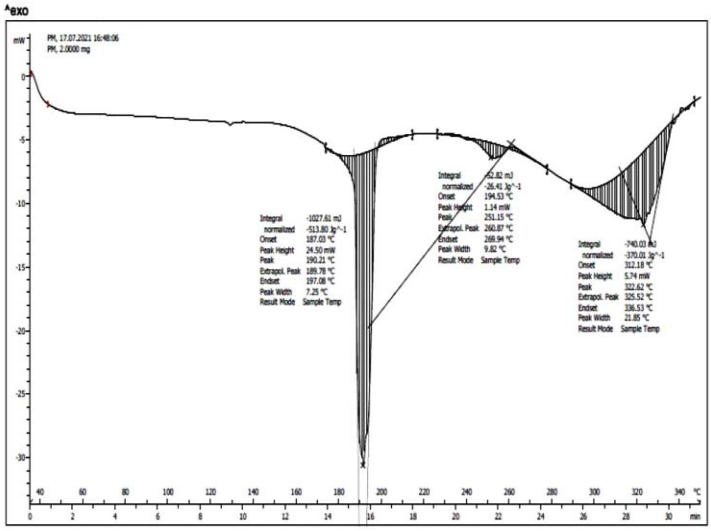

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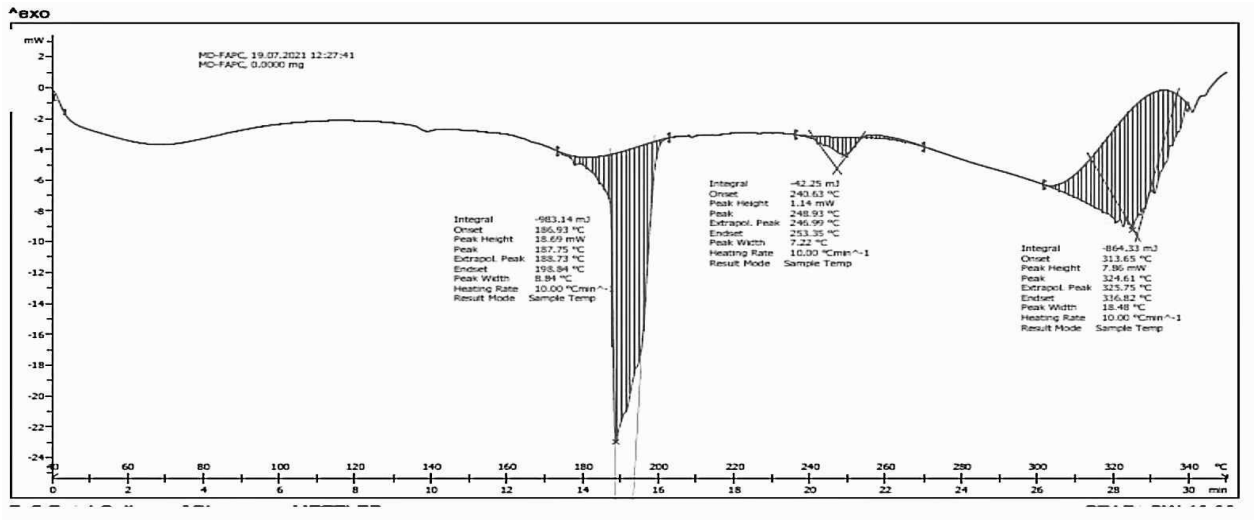


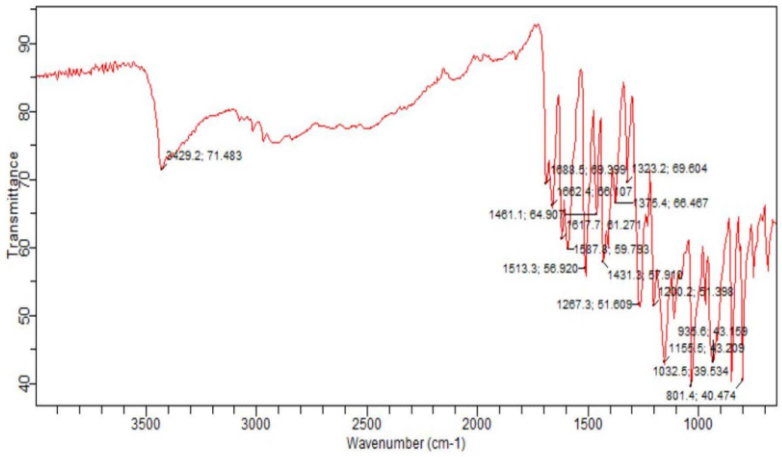
[E]

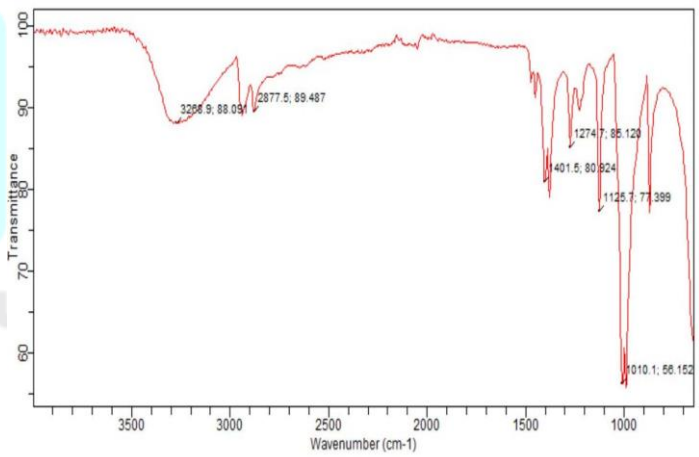
Fig. 4. Diffractogram of A. Ferulic acid B. pentaerythritol

C.LIPOID® S 100 D. PM E. MD-FAPLC

Fourier transform infrared spectroscopy (FTIR)

FT-IR analysis provides vital information about functional group identification and their interaction with other components used in the formulations. Fig 1 shows the FT-IR spectrum of FA, pentaerythritol, LIPOID® S 100, PM, respectively. The FT-IR spectrum of FA fig 1A shows the presence of absorption peak at ~3436.6 (OH stretching), 1617.7 (C = C stretching), 1461.1 (C = C aromatic stretching vibration), 1688.5 (C = O stretching), 1662.4 (C = C stretching). Pentaerythritol spectrum (Figure 1B) reported absorption peaks at 3268.9 (-OH stretching), 2877.5 (asymmetric C-H stretching), 1274.7 and 1125.7 (C-C stretching), 1010.1 (C=O stretching) The FT-IR spectrum of lipoid s100 displays in fig1C. LIPOID® S 100 showing the characteristics absorption peak at 2926.0and 2855.1 (C-H stretching of long fatty acid chain), 1736.9 (C = O stretching of fatty acid ester) 1651.2 (c-c stretching).





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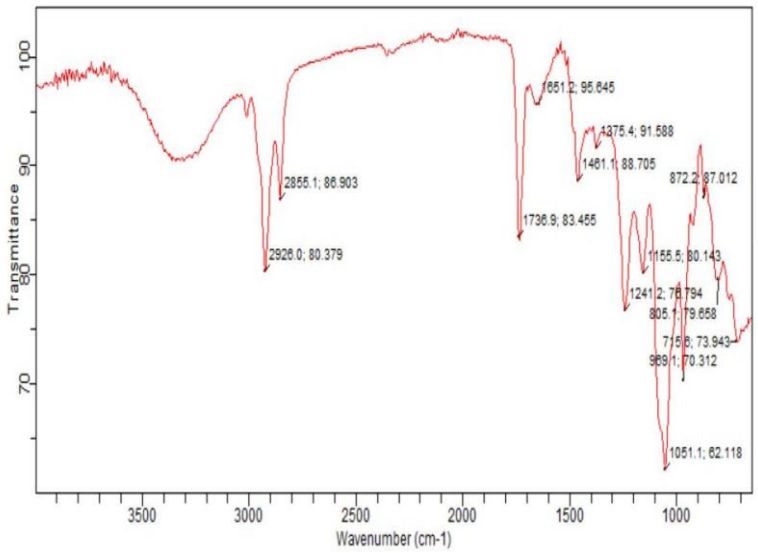

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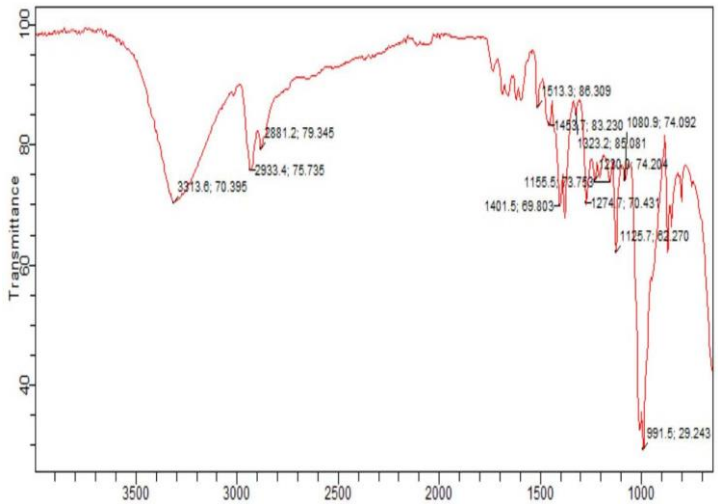

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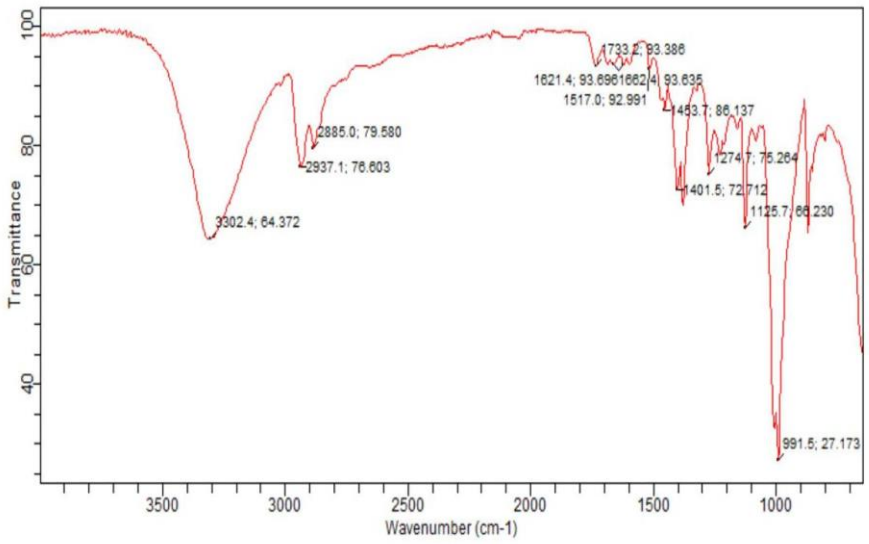

[E]

Fig .5.FT-IR of A. Ferulic acid B. pentaerythritol

C. LIPOID® S 100 D. PM E.MD-FAPLC

Solubility studies

Table No. 8. Solubility studies

Sr no	sample	Aqueous solubility (mg/mL)	n- octanol solubility (mg/mL)
1	FA	0.76±0.08	1.89±0.46
2	PM	3.5±21.05	5.12±1.53
3	MD-FAPC	7.85±2.06	9.56±2.65

The solubility analysis of FA, physical mixture PM and MD –FAPLC in water or n-octanol are shown in table. The pure FA showed low aqueous solubility around ~0.76mg/mL, whereas, in n-octanol, the solubility of FA was increased ~1.89 mg/mL respectively. The obtained results are not surprising because FA is a BCS II drug, which shows low solubility and high permeability. The PM exhibits higher aqueous solubility and n-octanol solubility around ~3.52 and ~5.12 mg/mL compared to pure FA. This could be attributed to close contact of negative charge (C=O) of FA and positive charge (N+) of phospholipid followed by their interaction resulted in modest enhancement of aqueous solubility of FA. The MD-FAPLC revealed higher aqueous solubility around ~7.85mg/mL (8-fold higher) compared to pure FA and PM. The solubility result was found significant ($p < 0.05$). This improved aqueous solubility could be explained by the following mechanism i.e. close association, interaction, dispersion, and followed by amorphization of FA due to the amphiphilic nature of LIPOID® S 100. Moreover, it may be also suggested that the enwrapping of two long fatty acid chains of LIPOID® S 100onto the polar head of LIPOID® S 100 enclose with FA resulted in maximum dispersion and amorphization of FA, which could result in enhancing aqueous solubility.

Dissolution studies

Before the oral drugs permeate the biological membranes of the gastrointestinal tract to reach the systemic circulation, the must firstly dissolve in gastrointestinal fluids. Drugs with poorly aqueous solubility exhibit low dissolution, leading to poor oral bioavailability. Therefore, enhancing the dissolution of poorly aqueous soluble drugs is a key problem in pharmaceutical research. Fig.6 shows the dissolution profile of ferulic acid from pure ferulic acid , physical mixture (PM), pentaerythritol , and MD-FAPLC in phosphate buffer (pH 6.8), respectively. The drug dissolution of MD-FAPLC was 8.2% within the first 10 min, while that of pure ferulic acid and physical mixture was only about 2.2% and 3.1% within the same time frame, demonstrating that the dissolution rate of MD-FAPLC was higher than that of ferulic acid and physical mixture. The dissolution of ferulic acid from MD-FAPLC was significantly enhanced in comparison with ferulic acid, and a physical mixture. The dissolution rate of MD-FAPLC was increase because, pentaerythritol as a hydrophilic material with good wettability could improve the dispersibility of FAPLC. Pentaerythritol also dissolution enhancer. Thereby increase the surface area of FAPLC. The phospholipids possessed the solubilisation and wetting properties, which contributed to the increased dissolution of ferulic acid. An amorphous state of ferulic acid in MD-FAPLC improved the aqueous solubility compared to the crystalline state.

Table No. 9.Cumulative dissolution profiles

Sr.no	Time (min)	% Release of FA	% Release of PM	%Release of MDFAPLC
1	0	0	0	0
2	10	2.2	3.1	8.2
3	20	4.68	4.95	12.15

4	30	7.52	8.61	16.56
5	40	11.18	15.42	21.36
6	50	16.51	20.36	26.37
7	60	20.96	23.87	35.12
8	70	25.43	30.41	42.15
9	80	30.24	34.92	51.63
10	90	35.42	40.06	62.31
11	100	38.22	43.73	71.54
12	110	40.52	48.56	75.49
13	120	41.27	54.69	81.47

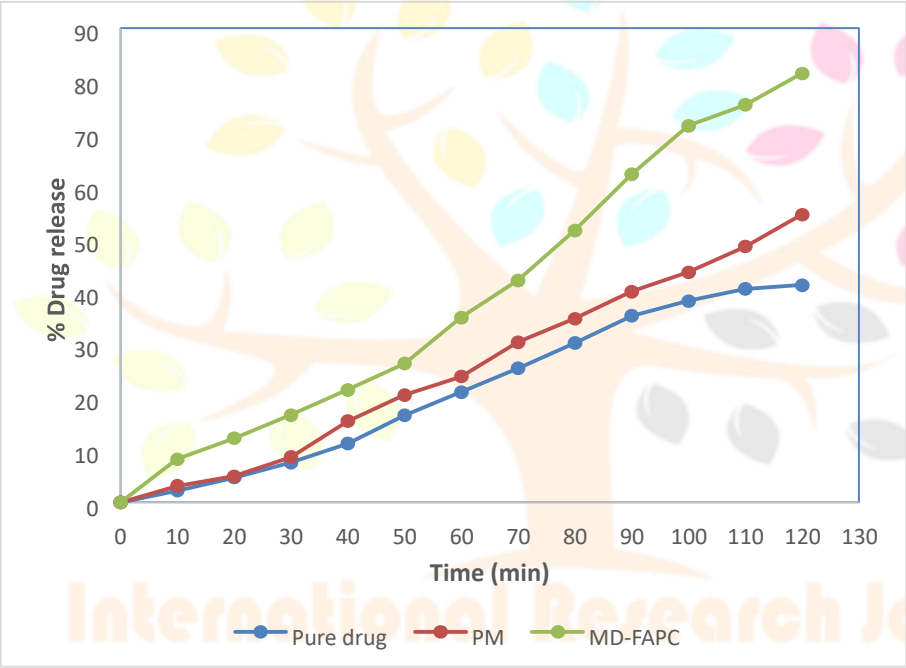

Fig.6. Cumulative dissolution profiles of a. ferulic acid b. physical Mixture c. MD-FAP

Conclusion and summary

In the present study, for the purpose of further enhancing the dissolution and oral bioavailability of ferulic acid based on phospholipid complex without destroying complexation state of ferulic acid and phospholipids, a novel matrix dispersion of ferulic acid based on phospholipid complex (FAPLC-MD) was prepared by the sonocomplex method. But sticky nature of PC because these lipid have a low melting point. These shows sticky nature at room temp.it shows aggregation and agglomeration non flowing characteristics which result in unsatisfactory dissolution and low oral absorption. In these case adding the matrix dispersion material the pentaerythritol is dispersion carrier. The pentaerythritol is a dispersion carrier. They was reported it pentaerythritol as dissolution enhancer and matrix dispersion agent. The pentaerythritol is reduce the sticky nature of the phospholipid complex also increase the dissolution of ferulic acid and also improve the oral bioavailability of ferulic acid. The combination ratio of ferulic acid, phospholipid and pentaerythritol (1:2:5). The 1:2 ratio maintain the integrity in GIT and prevent its degradation by GIT. These suitable interaction increase the drug release and also increase the bioavailability.

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