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Development and evaluation of 90% alpha lipoic acid coated with suitable polymers

Shiva Prasad*, Venkatesh, P K Kulkarni, Nagendra R, Hanumanthachar Joshi
Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysore, Karnataka, India

Abstract
LA-based nutraceuticals are in high demand right now, despite having a wide range of benefits, α-lipoic acid (ALA) is administered orally, which has pharmacokinetic restrictions that lower its therapeutic efficacy. ALA is well absorbed from the intestine however; ALA polymerises in acidic pH in the stomach. Hence the current study envisages coat particles or granules of ALA with, suitable polymers such as PVP/HPMC: these coats separate the drug from external gastric fluid it protect from polymerization and improve bioavailability. The present research started with the Preformulation studies on the active ingredient physical properties, compatibility of API with excipients by physical observation and FT-IR studies, DSC studies. The results showed that there was no interaction. The prepared granules were evaluated for Micromeritic properties. The formulation studies led to three formulas that presented a good flowability, considered adequate for the direct compression process. The percentage drug content was found in the range of 89 % to 91% for all the formulations, which was within the I.P acceptable limits. The solubility profiles of the formulations and the pure medication were compared in vitro. Formulations showed a higher rate of solubility than pure drug. The product subjected for 3 months accelerated stability study suggest that the drug is stable for a period of 3 months (stability study period) at accelerated condition, hence the study concludes that Alpha Lipoic acid can be formulated into a granulated ALA with a greater stability. LA coated with HPMC as granules were successfully produced using coating technology. HPMC has the ability to improve powder adhesion to the granule surface and promote film formation. With optimized temperature we could achieve a smoother surface and better coating uniformity for granules.

Keywords: Alpha lipoic acid, bioavailability, pharmacokinetic, granules, film-coated, stability

Introduction

Alpha-lipoic acid (ALA) is a fatty acid that is naturally produced by the body and found in some foods.[1] It has antioxidant properties, which means it can protect the cells from damage caused by free radicals. Some of the foods that contain ALA are red meat, organ meats, broccoli, spinach, tomatoes and Brussels sprouts.[2] ALA may have some benefits for various health conditions, such as nerve pain, skin aging, inflammation and metabolic disorders.[2] The IUPAC nomenclature of alpha lipoic acid is **(**R)-5-(1,2-dithiolan-3-yl) pentanoic acid. Another name for alpha lipoic acid is thioctic acid [3, 4], which reflects its structure as a cyclic disulfide with a carboxylic acid group. Alpha lipoic acid (ALA) is a molecule that has one chiral center at carbon 6, which means it can exist as two optical isomers or enantiomers: R-ALA and S-ALA [5]. These two forms are mirror images of each other and have different physical and biological properties. Alpha-lipoic acid (ALA) is acid sensitive because it has a pKa of 4.7. This means that it is 50% ionized at a pH of 4.7. At lower pH levels, such as in the stomach, ALA will be more ionized and therefore more unstable. This can lead to the breakdown of ALA and the loss of its beneficial effects. ALA is a reducing agent; it can donate electrons to other molecules. In the stomach, there are many oxidizing agents present, such as hydrogen ions (H+). These oxidizing agents can react with ALA and oxidize it, which can also lead to the breakdown of ALA. The preferred absorption site for alpha-lipoic acid (ALA) is the small intestine. ALA is a water-soluble and fat-soluble molecule; hence it can be absorbed by both the small intestine and the stomach. However, studies have shown that ALA is better absorbed in the small intestine than in the stomach. One study found that the bioavailability of ALA was 30% when it was taken on an empty stomach, but it increased to 40% when it was taken with food. The increase in bioavailability was likely since food helped to protect ALA from stomach acid and allowed it to be absorbed more efficiently in the small intestine. ALA is well absorbed from the intestine however; ALA polymerises in acidic pH in the stomach. Hence this drug needs enteric coats to prevent polymerization and facilitate absorption from intestine. Polymerization products presumably consisting of linear chains of 6,8-dithio octanoic acid inter connected by disulphide bonds. Hence the current study envisages to coat particles or granules of ALA with, suitable polymers such as CAP/ eudragit/HPMC: these coats separate the drug from external gastric fluid and it protect from polymerization and improve bioavailability.

Materials and methods

1. Materials

Alpha Lipoic Acid-USP was sourced from Jiangsu Tohope Pharmaceutical Co., Ltd. China, Hydroxypropyl Methylcellulose (HPMC) from Taian Ruitai Cellulose Co., Ltd. China, Povidone (PVP) from Star-Tech & JRS Specialty Products Co., Ltd. China, Methylene Dichloride (MDC) from Gujarat Alkalies and Chemicals Limited (GACL), Vadodara, Isopropyl Alcohol (IPA) from Deepak Fertilisers and Petrochemicals Corporation Limited, Bangalore, Starch Colorcon, Verna, Goa, Pre-Gelatinised Starch from Colorcon, Verna, Goa.

1.2 Manufacturing Stages

The raw materials Alpha Lipoic Acid and Binding agent (Pre-gelatinised Starch, Capsule TA starch) were sieved using #14 mesh. The Alpha Lipoic Acid and Binding agent (Pre-gelatinised Starch, Capsule TA starch) were pre-mixed using a Planetary Mixer. Coating solutions were divided into 2 solutions. Coating Solution -A: Coating agent (PvP) was taken in a beaker and dissolved in half of the Organic solvent (isopropyl alcohol) by warming in a water bath. Coating Solution -B: Coating agent (HPMC) was taken in another beaker and dissolved in the remaining half of the Organic solvent (isopropyl alcohol). Solution A was added to solution B, and MDC was added to the mixture. The mixture was then mixed well. The pre-mixed material was coated using the coating solution in a Planetary mixer for 4-5 minutes. The product was wet sieved using a 14# mesh. Lubricant (Magnesium stearate) was added and mixed using a Planetary mixer. The mixture was then sieved through a 14# mesh. The product was dried using a Tray dryer at 35°C. It was air-dried for 1 hour and then heat-dried until it reached the LOD. The product was dry-sieved using a 40# mesh.

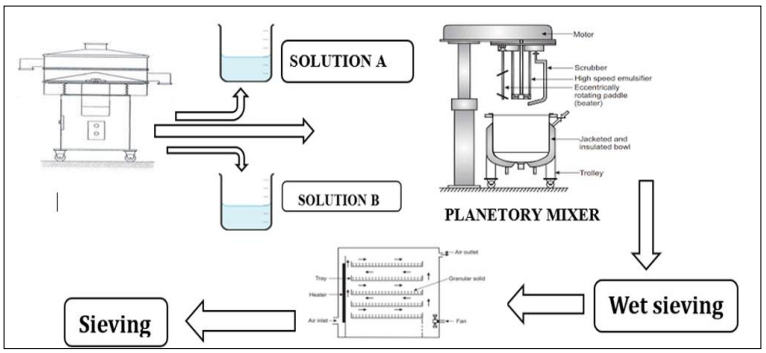


Fig 1: Process flow diagram

Table1: Formulation of Alpha Lipoic Acid 90%

SI. No.	Ingredients		(100 mg)	(500 mg)	
		F-I	F-II	F-III	F-IV
1.	Alpha Lipoic Acid-USP	91.00	91.00	0.455	0.455
2.	Pregelatinized Starch	4.00	4.00	-	0.0325
3.	Magnesium Stearate	2.50	2.50	-	-
4.	Hydroxypropyl Methylcellulose (HPMC)	1.50	1.50	0.0075	0.0075
5.	Povidone (PvP)	1.00	1.00	0.005	0.005
6.	Capsule TA Starch	-	-	0.0325	-
	Organic Solvents				
7.	Isopropyl Alcohol (IPA)	7.50	14.00	0.075	0.0375
8.	Methylene Dichloride (MDC)	7.50	7.50	0.0465	0.0375

Preformulation Studies

1. Organoleptic Properties

1.1 Color, Taste & Odor

The organoleptic properties like color, odor and taste of the API were evaluated.

1.2 Solubility Test [6]

100 mg of alpha lipoic acid was weighed and added to separate test tubes containing 10 mL of each solvent. The test tubes were capped and vigorously shaken for 1 minute. Subsequently, the test tubes were allowed to stand undisturbed for 1 hour. The absorbance of the solutions was then measured at λ max (270 nm) using a UV-Vis spectrophotometer.

1.3 Drug - Excipient Compatibility Studies

Compatibility study was performed by preparing blends of different excipients with ALA. The blends were stored at room temperature for 30 days. Physical observation is carried out at the initial stage, after 15 days and after 30 days.

1.4 Determination Of Λ Max.

UV-Vis spectroscopy was used to determine λ max of Alpha Lipoic Acid (UV-Vis spectrophotometer UV-1900i) in scan mode with the scanning range of 200-800 nm. Samples were prepared and placed in a quartz cuvette and read against blank at room temperature (25 ± 2ºC).

1.5 FT- IR *Spectral Analysis* [7]

Infrared spectra matching approach was used for the detection of any possible chemical interaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture compressed to form a transparent pellet using hydraulic press at 10 tons pressure and scanned between 4000 - 400 cm-1 in a Perkin elmer FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

Micromeritic Properties

1. Angle of Repose [8]

Angle of repose is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. The angle of repose is designated by θ. It was determined by funnel method. The powder blend was passed through funnel so that it forms a pile. The height (h) of the pile and the radius of the pile (r) were measured and angle of repose was calculated using following formula.

Tan θ = h/r
θ = Tan-1 (h/r)

Where,
θ = Angle of repose.
h = Height of the pile.
r = Radius of the pile.
The flow properties and corresponding angle of repose as per USP

1.2 Bulk Density and Tapped Density [9]
An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder was closed with lid, mounted onto the density determination apparatus (bulk density apparatus). The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and the operation was continued till the two consecutive readings are same. The bulk density and tapped density were calculated using the following formulae
Bulk density = W/V_0

Tapped density = W/V_f
Where,
W= Weight of powder, (gm)
V_0= Initial volume of powder, (ml)
V_f = Final volume of powder, (ml)

Measurement Of Powder Compressibility
a. Compressibility Index [10]
The term compressibility is the ability of powder to reduce its volume under pressure. The compressibility index of the powder was determined by the Carr's compressibility index. It is used as an indication of the flowability of a powder. A compressibility index greater than 25 is an indication of poor flowability and below 15 indicates good flowability.
Compressibility index = (Tapped density-Bulk density)/ (Tapped density)×100
"Stroke", in other words the maximum distance the plunger can travel in either an "IN" or an "OUT" direction, for example, 0 to 30 mm.

b. Determination of Hausner's Ratio
The hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ideal range should be 1.2 - 1.5. Hausner's ratio was determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Assay Of Alpha Lipoic Acid Coated 90% By HPLC Method
Weighed and transferred about 55.5 mg of sample to a 50 mL volumetric flask. Added 25 mL of mobile phase and soaked for 5 minutes. Sonicated for 5 minutes with periodic shaking, and made up the volume with mobile phase. Filtered through a 0.45 separately equal volumes of the standard and sample preparations. Recorded the chromatograms and measured the area for major peak.

Differential Scanning Calorimetry (DSC)
DSC measures the amount of heat energy absorbed or released by a sample, as it is heated, cooled or held at a constant temperature which intern provides the melting point of a sample. Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter, (Shimadzu limited) 0.45 μm syringe filter. If the material was more granular, crushed the material before weighing Injected.

***In Vitro* Drug Release Studies**
voltage output to 5V and draws 5V regulated power Drug release studies were carried out by using USP Type II paddle dissolution test apparatus at 100 rpm for 1 hr in 0.1 N HCl (900ml) maintained at 37°C ± 0.5ºC. 10 ml of sample was taken and analyzed by using UV spectrophotometer at 270 nm. Then the dissolution medium was replaced with 6.8 pH Phosphate buffer (900 ml) and tested for drug release for 1hr at 37°C ± 0.5ºC temperature and 100 rpm speed. After 5, 10, 15 and 45 minutes, 10ml samples were taken out and 10 ml volume of fresh phosphate buffer pH 6.8 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 270 nm.

Stability Studies
- The International Council for Harmonization (ICH) guidelines titled stability testing for new drug substances and product (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and United States of America. ICH guidelines specifies the length of study and storage conditions.
- Long term testing: 25 ± 2°C/60% ± 5% RH for 12 months.
- Accelerated testing: 40 ± 2°C/75% ± 5% RH for 6 months.

Procedure
Stability studies were carried out for formulations at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months. The selected clear ALU-ALU packed formulations were stored at 25±2°C/60%±5%RH and 40±2°C/75%±5%RH for 3 months and their physical appearance, average weight, assay, and in vitro drug release were evaluated at specified intervals of time (every month).

Results and discussion
1. Organoleptic Properties
The organoleptic properties like color, odor and taste of the ALA were evaluated. The color of Alpha Lipoic Acid was found to be Pale yellow to yellow crystalline powder. The color of alpha-lipoic acid can vary depending on the manufacturing process. It is typically pale yellow, but it can also be more yellow or even orange. The odor of alpha-lipoic acid is slight and characteristic. It is often described as having a nutty or caramel-like odor. The taste of alpha-lipoic acid is bitter. It is often described as having a metallic or sulfurous taste. Alpha Lipoic Acid showed similar color, taste, and odor as per the I.P specifications.

2. Solubility Test
The solubility studies of drug (API) revealed that Alpha Lipoic Acid was sparingly soluble in water, Propylene Glycol and soluble in methanol, ethanol and Dimethyl sulfoxide (DMSO).

3. Drug – Excipients Compatibility Studies

From the drug excipients compatibility study, it was observed that there was no characteristic change found between drug and excipients. Thus, it was concluded that the excipients selected for the formulation were compatible with Alpha Lipoic Acid and suitable for formulation development.

Determination of λ max.

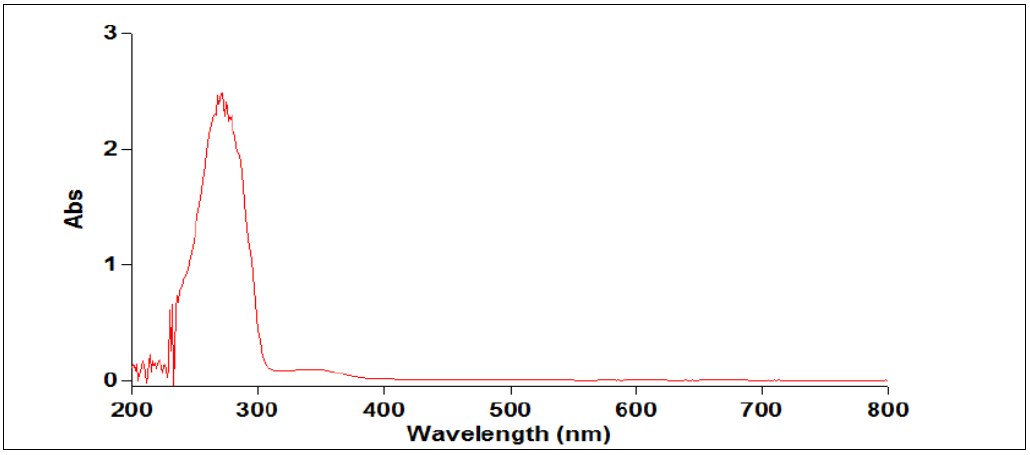


Fig 2: Peak representing absorption at 270nm

Standard calibration plot.

Absorbance's of all the solution were taken at 270 nm against blank and calibration curve was constructed by taking concentration on x-axis and absorbance on y-axis. As shown in fig- 3

Table 2: Standard calibration data of ALA

Concentration (µg/ml)	Average Absorbance (λ at 270 nm)
0	0
2	0.1606
4	0.3165
6	0.4740
8	0.6266
10	0.7340
12	0.9268

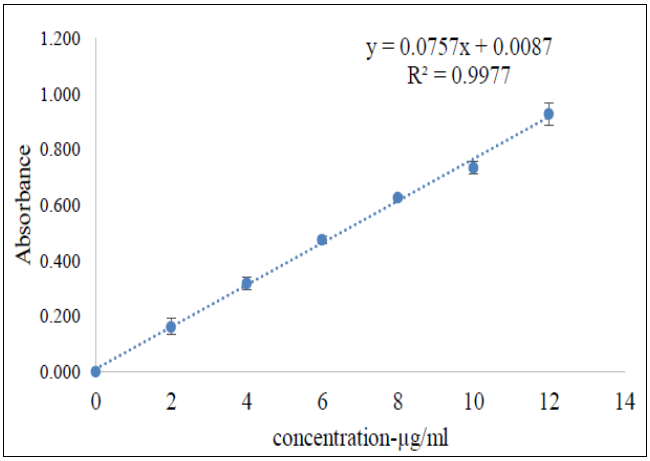


Fig 3: Standard calibration plot of ALA

Absorbance's of all the solution were taken at 270 nm against blank and calibration curve was constructed by taking concentration on x-axis and absorbance on y-axis. As shown in fig- 3

Obtained peak were similar to reported peaks as 270 nm in USP. This value was selected for rest of the analysis. Lambda max refers to the wavelength along the absorption spectrum where a substance has its strongest photon absorption or the presence of chromophores (light-absorbing groups) in a molecule.

3.4 FT-IR Spectral Studies

FT- IR studies of the pure Alpha Lipoic Acid, excipients and combination of drug and excipient was carried out to find any interaction between drug and excipients used in the formulation. FT-IR study was performed using IR spectroscopy (Perkin Elmer). The I.R spectra of drug and excipients were shown in Fig. 4 to respectively.

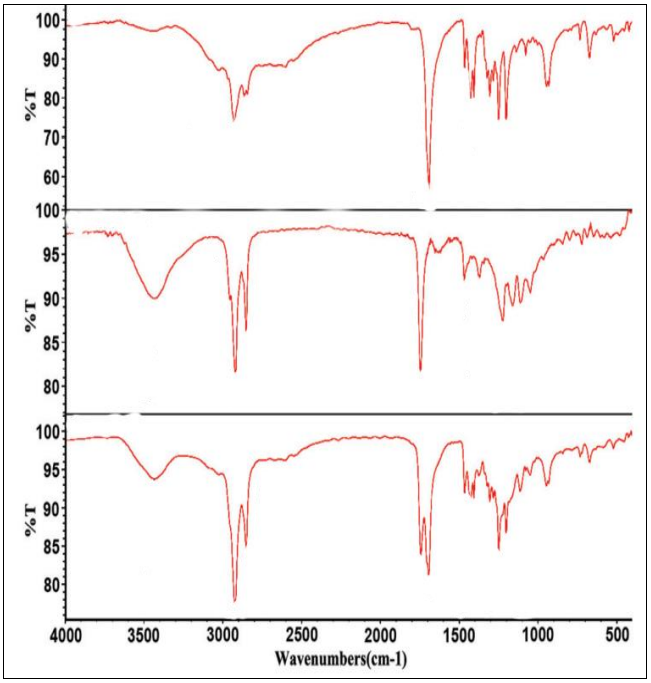


Fig 4: A. FT-IR spectra of Formulation F-I,

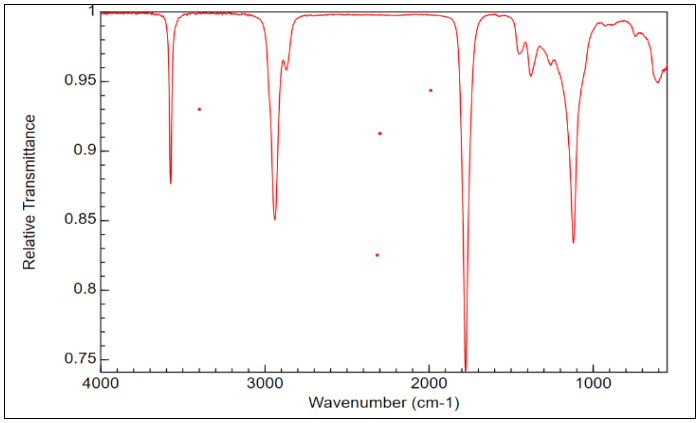


Fig 5: FT- IR Spectrum of Pure ALA

B. FT-IR spectra of Formulation F-II,
C. FT-IR spectra of Formulation F-III,
D. FT-IR spectra of formulation F-IV.

Compounds	Functional Groups				
	C=O stretching	C-H stretching	C-O-C stretching	C=O bending	C-H bending
Pure Alpha Lipoic Acid	2,335	1,750	1,360	1,240	1,020
F-I	2,334	1,747	1,360	1,234	1,020
F-II	2,336	1,750	1,359	1,240	1,020
F-III	2,335	1,734	1,360	1,240	1,017
F-IV	2,335	1,750	1,360	1,240	1,020

FT-IR spectroscopic studies indicated that the drug is compatible with all the excipients. The FT-IR spectrum of physical mixture showed all the characteristic peaks of Alpha Lipoic Acid, thus conforming that no interaction of drug occurred with the components of the formulation.

Micromeritic Properties

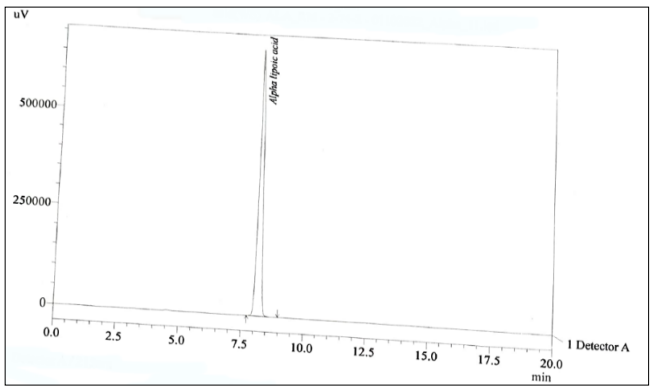
Table 4: Alpha Lipoic Acid powder blends were evaluated for different precompression parameters and the results are mentioned in

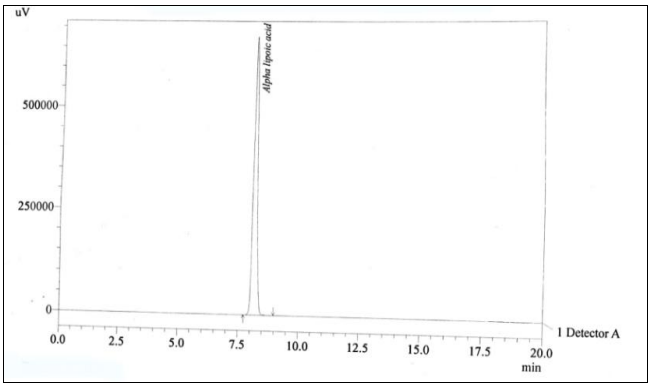
Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio
F-I	28.56±0.3	0.562±0.2	0.690±0.5	18.55±0.7	1.15±0.7
F-II	30.09±0.7	0.640±0.1	0.745±0.3	14.09±0.2	1.16±0.6
F-III	25.46±0.2	0.305±0.3	0.351±0.5	13.11±0.1	1.15±0.2
F-IV	24.23±0.6	0.317±0.7	0.367±0.1	13.63±0.6	1.15±0.5

*All the values are expressed as mean ± SD, n=3

Angle of repose of Alpha Lipoic Acid powder blend was found in the of 24º.23' to 30°.09'. These values are well within the limit of 25º – 30° which indicates the flow of Alpha Lipoic Acid was excellent. The above results revealed that the all the formulations (F-I to F-IV) possess excellent flow. Bulk density of Alpha Lipoic Acid was found between 0.305 ± 0.3 to 0.640 ± 0.1 g/cm^3. Tapped density ranges between 0.351 ± 0.5 to 0.745 ± 0.3 g/cm^3. Compressibility index values was found to be in the range of 13.11 ± 0.1 to 18.55 ± 0.7 % and the hausner's ratio lies between 1.15 ± 0.2 to 1.16 ± 0.6. Compressibility index of formulation - I belongs to fair flow and compressibility index of other formulations indicates that the blend belongs to good flow property.

3.6 Assay of Alpha Lipoic Acid By HPLC Method





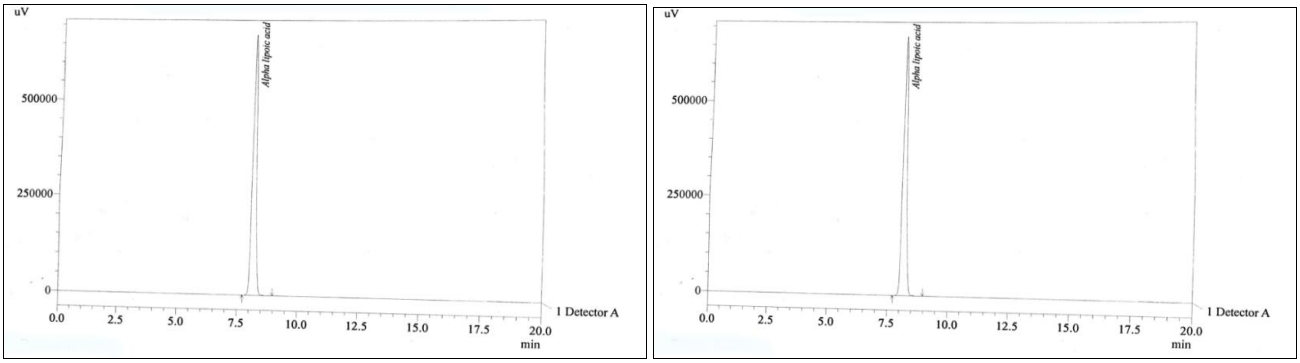


Fig 6: HPLC Chromatogram of Formulation F-I-F-IV

Differential Scanning Calorimetry

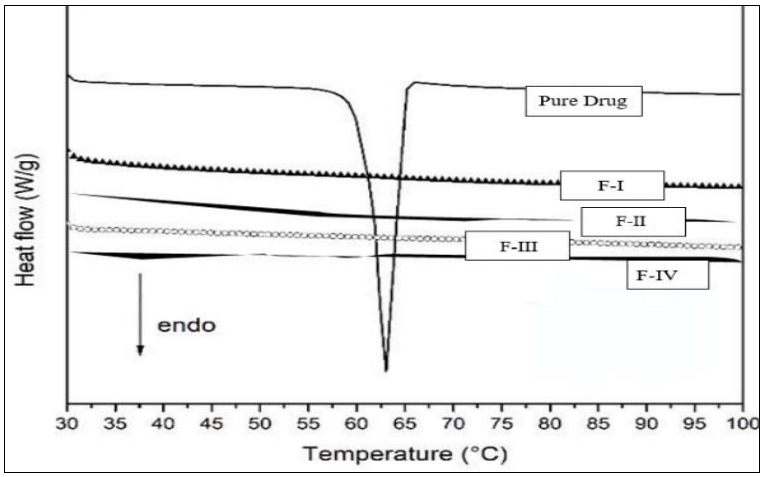


Fig 7: Differential scanning calorimetry (DSC) scans of Pure Alpha lipoic acid (ALA) and Formulations (FI-IV). Samples were placed under the air flow for scanning and heating from 30 °C to 100 °C at 3 °C/min.

In the thermogram of crystalline ALA reported in Fig.7 it is clearly visible a sharp endothermic peak at 66 °C (ΔH = −136.17 J/g) corresponding to the melting, following the degradation of the compound whereas DSC of Formulations (F I-IV) did not showed any peaks which indicates drug is distributed in the polymer during the formulation.

In Vitro Dissolution Studies

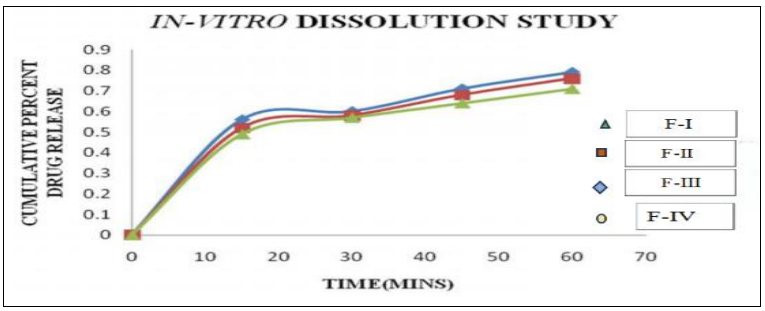


Fig 8: Cumulative Percentage of Release of ALA in 0.1N HCL

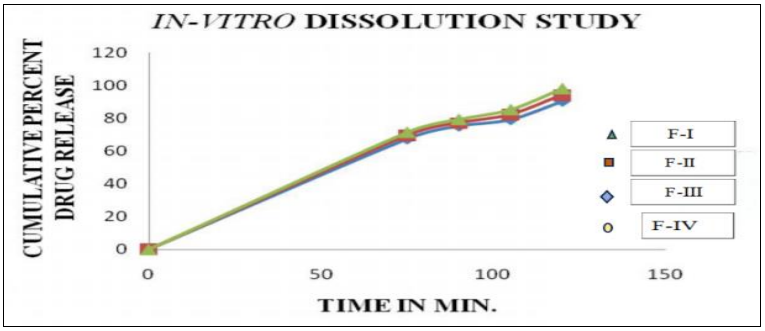


Fig 9: Cumulative Percentage of drug Release of ALA Formulations in phosphate buffer pH 6.8

In-vitro comparision of dissolution profile were carried out for the formulation F1,F2,F3,F4 and for the pure drug. At the end of 60 minutes percentage cumulative drug realease from pure drug was found to be 49.28%. In-vitro drug realease studies carried out using USP type II dissolution aparatus (Paddle type). Formulations exhibited better dissolution rate when compared with pure drug. The cumulative drug realease was increased when the optimum amount of stabilizing agent was used and the reason might be because of stabilizing agent, better solubility.

Stability Studies

The stability study was done for Formulations and stored at 25±20ºC/60%±5% RH and 40±20ºC/75% ±5% RH for 3 months. Stability studies revealed that there was no significant changes found in physical appearance, in vitro drug release and assay during the period of three months even after stored at 25±2ºC/60%±5% RH and 40±2ºC/75%±5% RH. The study revealed that the formulation F-I-IV was stable at 25±2°C/60%±5%RH and 40±2ºC/75%±5% RH even after stored for three months.

Conclusions

In order to develop a HPMC coated granules of alpha-lipoic acid, a micronutrient with several pharmacological as well as antioxidant properties, we have performed the pharmaceutical development taking into account technological and dissolution aspects-compared to the uncoated ALA. The present research started with the Preformulation studies on the active ingredient physical properties, including assay, content uniformity, angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, and dissolution. The formulation studies led to three formulas that presented a good flowability, considered adequate for the direct compression process.

ALA coated with HPMC as granules were successfully produced using coating technology. HPMC has the ability to improve powder adhesion to the granule surface and promote film formation. With optimized temperature we could achieve a smoother surface and better coating uniformity for granules.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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