**Abstract**

 Thioctic acid is a well known drug used for the treatment of both autonomic and peripheral diabetic neuropathy. It is a natural antioxidant which neutralizes free radicals including oxygen radicals and ionized metals. Thioctic acid (TA) is absorbed via the stomach and gut, and can easily be supplemented orally.

 It is well known that the flowability is one of the most important factors in drug development. Inadequate flow properties of solids can cause serious problems during pharmaceutical unit operations (e.g. compression, filling, conveying). Of particular interest is segregation, which can be very complex in terms of its cause and compounding. Powder flow is most frequently thought of as relevant to formulation development, and it was attempted to correlate any one of a number of measures of powder flow to the manufacturing properties in formulation.

 Therefore the aim of this work is to overcome the poor flowability of thioctic acid in order to formulate it as compressed tablets with low production costs, compatible excipients and improved quality and bioavailability.

 Thus the work in this thesis is divided into four chapters

**Chapter I:** Preformulation Study of Thioctic acid

**Chapter II**: Formulation and Evaluation of Thioctic acid Tablets.

**Chapter III**: Stability Study of the Selected Thioctic acid Tablets.

**Chapter IV**: Bioequivalence Study of the Selected Thioctic acid Tablets.

**Chapter I**

**Preformulation Study of Thioctic acid**

The work in this chapter includes:

**1-Compatability Study of Thioctic acid with Different Excipients:**

 The work here included preparation and storage of drug-excipient mixtures with subsequent evaluation of the possible interactions of thioctic acid with the tested excipients. Samples prepared by gentle mixing of the drug and each of the used excipients namely Avicel PH101, Aerosil 200, Explotab, Ac-Di sol, Tablettose , Magnesium stearate, Maize starch, Poloxamer 188, Emcompress, Spray dried lactose and Lactose monohydrate in (1:1) ratio in glass mortar. 500 mg of each mixture was accurately filled into individual glass vials and tightly sealed. Vials containing thioctic acid or excipients alone were also prepared. The prepared samples were stored at temperatures of 30, 40 and 50º C for two weeks. The stored samples were evaluated by daily visual examination, DSC, IR and TLC.

 The results revealed that the plain drug stored at the stated temperatures for two weeks, showed no changes in its physical appearance. The fresh and stored mixtures of thioctic acid with most of the tested excipients showed no change in color and/or appearance up to the end of the storage period which is a good preliminary step of physical stability. Mixture of thioctic acid with Aerosil showed discoloration after 4 days of storage at 50° C. Whereas, its mixture with Poloxamer 188 showed liquefaction after 3 days of storage at 50°C.

 The DSC thermogram of the fresh thioctic acid showed one main prominent sharp characteristic endothermic melting peak at about 62.87°C. Thioctic acid stored at 50°C for two weeks showed no major changes in the endothermic melting peak temperature or enthalpy, which may indicate drug stability. Furthermore the sharp peak indicated the crystalline nature of the drug.

Based on the DSC and IR results, no interaction was observed between thioctic acid and Maize starch, Ac-di-sol, Explotab, Magnesium stearate, Spray dried lactose, Lactose monohydrate, Emcompress and Tablettose. However, the DSC thermograms of Avicel PH101, Aerosil and Poloxamer 188 were not discriminative as the thermograms of these excipients alone showed characteristic melting peaks within the temperature range where the characteristic melting peak of the plain drug occurred. No conclusion could be made about compatibility of thioctic acid with these excipients due to the overlapping; the compatibility therefore confirmed by further IR investigations, which confirm the absence of interaction between drug and Poloxamer 188 or Avicel PH101. While, it confirmed the presence of a chemical interaction between the drug and Aerosil where the IR spectrum of the drug with Aerosil, showed a decrease in all peak intensities and some changes in the finger print region.

 Thin layer chromatographic analysis for plain thioctic acid and its physical mixtures with the mentioned excipients showed that the Rf values are nearly equal in all cases.

 Finally, from the previous drug-excipients compatibility study, the following excipients were proved to be candidates for the drug formulation: Avicel PH101, Maize starch, Explotab, Ac-Di sol, Emcompress, Tablettose, Magnesium stearate, Spray dried lactose, Lactose monohydrate and Poloxamer 188.

**2- Improvement the Flowability of Thioctic acid:**

In order to overcome the poor flowability of thioctic acid and formulate it in the form of conveniently compressed tablets; granulation as well as solvent deposition would be carried. Choosing of excipients was based on the previously mentioned drug-excipient compatibility studies, additives which showed adequate physical and chemical compatibility with thioctic acid were used in the formulation. Two super disintegrants were chosen; Ac-di sol and Explotab. Magnesium stearate was used as a lubricant. Finally, fillers used were Maize starch, Avicel PH101, Tablettose, Spray dried lactose, and Emcompress. Thioctic acid powder formulations, each 500 mg containing 300 mg of the drug were prepared.

**A.Granulation of Thioctic acid**: which carried out by several methods:

**1-Wet Granulation**: where a mixture consisted of 300 mg of thioctic acid, 145 mg of diluent, 50 mg of super disintegrants and 5 mg Magnesium stearate as a lubricant was prepared. As the diluent and half the calculated amount of the disintegrant were weighed and mixed intimately by geometric dilution.The granulating solution of the binder; 5% (w/v)starch pastewas prepared**.** Then the powders and the starch paste were kneaded to proper consistency. The wet mass was forced through a sieve No. 18 (1 mm) and the resulted granules were dried in an oven at 30 ◦C. The dried granules were screened to suitable size through a sieve No. 25 (710 µm) and finally the lubricant and the remaining amount of the disintegrating agent were mixed with the granules.

**2-Dry Granulation**: where a mixture consisted of 300 mg of thioctic acid, 145 mg of diluent, 50 mg superdisintegrant and 1% lubricant was prepared. The drug, the diluent, and the disintegrant were weighed and mixed intimately by geometric dilution. The mixture was then compressed into large slug; using a single punch machine , which are then broken and passed through sieve No.18 (1mm) and No.25 (710 µm). The unused fine material was reworked to avoid waste. Then the lubricant was added finally.

**3-Melt Granulation**: a mixture consisted of thioctic acid 300 mg, Poloxamer 188, 115 mg and Lactose monohydrate 30 mg (as 6 % w/w) was prepared. The drug and the diluent were mixed and heated up to 50 ◦C. Poloxamer 188 was heated separately to 65 ◦C, thus it was added in the molten form to the substrate and then the mixture was mixed with a magnetic stirrer for 5 min. At the end of the granulation process, the prepared granules were cooled at room temperature by spreading them out on trays, collected and passed through sieve No 25 (710 µm) and then 10% of the used disintegrant and 1% lubricant were added (M2).

 The solid dispersion was prepared by fusion; where Poloxamer 188 was melted, then the drug and Lactose were added. The mixture was stirred for 5 min. at 50ºC, and then cooled on an aluminum foil at room temperature. The solid sample was then pulverized in a mortar, forced through sieve No 18 (1mm) , and stored in a dessicator at 25±2 ◦C, then passed through sieve No. 25 (710 µm) ; 10% disintegrant and lubricant were added (M1).

 For comparison; the physical mixture was prepared by mixing the thioctic acid, Poloxamer 188 and Lactose monohydrate in a glass mortar with a pestle for 10 min (MP).

**B-Freeze Drying:** It is a granulation technique that converts liquids into dry powder by sublimation producing highly flowable powder in comparison of non-treated powder.

A solution of thioctic acid alone in ethanol was subjected to freeze drying in the lypholizer, where a solution of the drug in ethanol was freezed at -20 °C and then was left in lypholizer at -50 °C for 24 hours.

300 mg of freeze dried thioctic acid were mixed with 145 mg of the used fillers in addition to 50 mg disintegrant and 1% Magnesium stearate in each formula as a lubricant (formula S1-S10). The drug, the diluent, and the disintegrant were weighed and mixed intimately by geometric dilution in a porcelain dish.

**C.Solvent Deposition of Thioctic acid**: Where the enhancement of the flow properties of the solvent deposition systems was due to the effects of free flowable properties of the carriers. Thioctic acid deposited on carriers by solvent deposition system. The carriers used were: Avicel PH101, Maize starch and Spray dried lactose as A1, A2 and A3; respectively. Each in (1:0.5) (w/w) drug: carrier ratio. The calculated amount of thioctic acid was dissolved in an amount of ethanol sufficient to impart good wetting for each carrier separately. This solution was added to each carrier while mixing until homogenous wetting was attained. The obtained slurry was stirred by a magnetic stirrer at room temperature till all the solvent (ethanol) evaporated, the formed mass was transferred to desiccator and stored till completely dry. The solid mass was then pulverized in a mortar and the particles which passed through sieves No. 18 (1mm) and No. 25 (710 µm, were mixed with 10 % Explotab and 1% Magnesium stearate.

**3- Evaluation of the Flowability of Thioctic acid and Its Powder Formulations:**

The flowability of thioctic acid alone and after formulation was determined by:

**1-Determination of the angle of repose:** as tan θ= h / r**.**

**2-The compressibility index and Hausner ratio:**

Carr’s index (Ci) =[(ρt - ρ°)/ ρt] x 100

Hausner ratio = ρt / ρ°

Where ρ° and ρt were the initial and tapped densities respectively, were calculated by dividing the weight of the powder by the corresponding initial or tapped volume recorded.

 All the parameters indicating poor flowability of thioctic acid, as the drug has angle of repose equal to 39˚, Carr’s index more than 40% and Hausner ratio more than 1.25.

 The granules prepared by dry granulation method showed excellent flowability than those prepared by wet and melt granulation.

 Among the different granulation techniques, freeze drying method produces highly flowable powder in comparison of non-treated powder.

 The flowability of the thioctic acid from the Avicel PH101 system (formula A1) was comparatively higher than the other systems. This was attributed to the smaller particle size of the thioctic acid in the Avicel system and higher flowability of the carrier itself.

 From the previous results, it can be concluded that; the formulae W9, D2, M2, A1, S7 possess the highest flow properties in comparison to the other formulae as well as the thioctic acid powder, indicated by Carr’s index which was less than 15 %, Hausner ratio which was close to one and angle of repose which was less than 28˚. Therefore they would be selected for compression into tablets and for further study.

**Chapter II**

**Formulation and Evaluation of Thioctic acid Tablets**

The work in this chapter includes:

**A-Chromatographic Scanning of Thioctic acid using HPLC:**

Mobile phase was a filtered and degassed mixture of methanol, 0.005 M phosphate solution, and acetonitrile (1160:920:180).Internal standard; was prepared by dissolving 10 mg of Methyl paraben in 100 ml mobile phase then transfer 10 ml to 100-ml volumetric flask to obtain a solution of a concentration (10μg/ml). Stock standard solutionwas prepared by dissolving 100 mg of thioctic acid in 100 ml of the mobile phase, to obtain a solution having a concenteration of about 1mg/ml. The liquid chromatograph is equipped with spectrophotometric detector. The flow rate is 1.2 ml /min. Equal volumes (20 μl) of the internal standard and the prepared solution were injected into the chromatograph, the chromatograms were recorded. A typical chromatogram for Thioctic acid was detected at λ 215 nm. Thioctic acid and methyl paraben were well separated and their retention times were 6.3 and 3.6 min, respectively. Both peaks were sharp and symmetrical with good baseline resolution and minimal tailings, thus facilitating accurate measurements of the peak area ratios. Methyl paraben is a good internal standard because of its adequate retention time and similar spectral properties to Thioctic acid.

 **B-Construction of the Calibration Curve of Thioctic acid using HPLC:**

 Mobile phase, chromatographic conditions and internal standard conditions as mentioned earlier.

 Stock solution of thioctic acid was prepared by dissolving 100 mg thioctic acid in 100 ml of the mobile phase to obtain a solution having a concenteration of (1 mg/ml). Standard samples were prepared by transferring aliquots of thioctic acid solution at concentration ranging from 10-320 µg/ml into 10ml volumetric flasks. An aliquot of the internal standard equivalent to 100µg was transferred to 10ml flask; the flasks were brought to volume by the mobile phase and mixed thoroughly, then filtered through a millipore filter of 0.45µ pore size. Three 20µl injections of each standard solution of thioctic acid containing the internal standard were made. According to the predetermined wavelength, the detection was at λ 215 nm. The peak area ratios of thioctic acid-methyl paraben were plotted against thioctic acid concentrations.

The plot was highly linear (r = 0.9999) and the regression analysis of the data gave the slope and intercept as follows:

Y = 0.015X - 0.0021

Where, Y and X are the peak area ratio (Drug / Internal standard) and the thioctic acid concentration, respectively.

 **C- Preparation of Thioctic acid Tablets**

 The selected powder formulae from the previous chapter; W9, D2, M2, S7 and A1 were compressed into tablets using single punch machine and concave 12 mm punch and die set. The weight of each tablet was 500 mg containing 300 mg thioctic acid.

**D-Evaluation of the Prepared Thioctic acid Tablets**

The prepared thioctic acid tablets as well as the commercial Thiotacid® tablets were evaluated for:

**1- Determination of Weight Variation:**

Ten tablets were separately weighed and their average weight and standard deviation were calculated.

All the prepared tablets showed acceptable weight variation ranged (from 495 to 505 mg) with standard deviation less than 2%.

**2- Uniformity of Tablets Thickness and Diameter:**

The diameter and thickness of ten tablets were measured at two different positions. The average value was then calculated.

All tablets had thickness ranged from 3 to 3.15 mm and diameter nearly of 12 mm, indicating uniformity in the prepared tablets.

**3- Content Uniformity:**

Ten tablets were used in this test, where each one was crushed and transferred into 50-ml volumetric flask. The flasks were brought to volume by methanol (HPLC grade), the flasks were mechanically shaken for 5 minutes, 5ml of the solution was removed into a centrifuge tube and centrifuged at 3000 rpm for 5 minutes. The supernatant was filtered through a millipore filter of 0.45mm pore size; the first 20 ml of the filterate were rejected then, 0.1 ml of the filterate was diluted with 10 ml mobile phase. One ml aliquot of the prepared solution was transferred to a 10 ml volumetric flask, 0.2 ml internal standard solution was added and the volume was completed with the mobile phase. The samples were filtered through a 0.45 µm membrane filter (millipore) and degassed. The mobile phase was filtered and degassed mixture of 0.025 M phosphate solution and acetonitrile (62:38).

The liquid chromatograph is equipped with 220 nm detector and a 3.9 mm × 30 cm column that contains packing L. the flow rate was 1.5 ml per minute.

 The unknown concentration of the drug in each tablet was calculated using the following equation:

Q = (R/A + B) x dilution factor

Where, Q is the drug concentration, R is the peak area ratio (drug/internal standard), A is the slope of the calibration curve and B is the Y-intercept.

All tablets showed drug content ranged from 98.3 to 99.7 %of the initial drug content added. The percentage deviation did not exceed 2% indicating well-mixed products.

**4-Determination of Tablets\_Friability:**

Ten tablets from each formula were accurately weighed and placed in the drum of the friabilator, the drum was rotated at 25 r.p.m for a period of 4 minutes. The tablets reweighed and the percentage weight loss was determined.

All tablet formulations exhibited percentage weight loss ranged from 0.01 to 0.2%. It was found that, in general, these values are extremely low and comply with the friability requirements of USP.

**5- Determination of Tablets Hardness:**

The average breaking strength (in Kg) of ten tablets of each formula was determined by the hardness tester.

All tablet formulations showed good breaking strength within the range from 5.9 to 8.3 Kg, which are acceptable within the limit of conventional tablets.

**6- Hardness/Friability Ratio (H.F.R):**

The H.F.R for each formula was calculated by dividing the average hardness by its mean friability. It is a good criterion for the mechanical strength of tablets. The prepared formulae could be arranged in an ascending order of their mechanical strength as follows:

D2 < W9 < S7 < Thiotacid® < M2< A1

**7- Determination of Tablets Disintegration Time:**

A tablet was inserted in each of six cells of the disintegration apparatus. The immersion fluid used was 0.1N HCL at 37± 0.5°C. Disintegration time was recorded at which the tablets disintegrated leaving behind no aggregates on the basket mesh.

Formula M2 showed the highest disintegration time about 600 seconds, while formulae D2 and S7 had shorter disintegration time of 70 and 130 seconds, respectively. The formulae could be arranged in a descending order of their disintegration time as follows:

 M2> W9 >Thiotacid® > A1 > S7 > D2

**8- Dissolution Testing of Thioctic acid from Its Tablet Formulations:**

The dissolution of thioctic acid from different tablet formulations was tested by using USP dissolution tester, apparatus (2). The paddle was made to rotate at 75 revolutions per minute (rpm). The dissolution medium was 900ml 0.1N HCL at 37± 0.5°C.

 Mobile phase and chromatographic system proceeded as directed in the test for the content of thioctic acid.

Standard solution prepared by dissolving 300 mg of thioctic acid in 900 ml 0.1N HCL.

At predetermined time intervals 5, 15, 30, 45 and 60 minutes, 5 ml sample was withdrawn and filtered through a 0.45 mm millipore filter and analyzed for thioctic acid. The withdrawn samples were replaced by equal volume of dissolution medium to maintain a constant volume.

 About 20 μL of each of the standard solution and the test solution were injected into HPLC apparatus. The detected peak areas at λ 220 nm were measured. All results were run in duplicates. In each time the mean of three determinations was used to calculate the drug release from each of the prepared tablet formulations.

 The percentage of thioctic acid dissolved in each sample was determined by the formula = (Peak area of the test / peak area of the standard) × 100

All formulae showed acceptable dissolution, where more than 85% of the labeled dose is dissolved in 45 minutes except the formula M2 where only 59% of the labeled dose is dissolved. Formula D2 showed the highest dissolution and the lowest disintegration time, this proves that recompressed tablets are weaker than compressed ones. And also prove that tablets prepared from slugged granules disintegrate and dissolute faster than tablets of wet granules using starch paste. While the formula M2 showed the lowest dissolution rate and the highest disintegration time.

The formulae could be arranged in a descending order according to the amount of the drug dissoluted after 45 minutes as follows:

D2 > S7 > W9 > A1 > Thiotacid® > M2

**9- Kinetic Analysis of the Dissolution of Thioctic acid from its Tablet Preparations:**

The dissolution data were analyzed using linear regression according to zero-order and first-order as well as Higuchi diffusion model. It was revealed that the dissolution of the drug from all the formulations as well as Thiotacid® tablets follows zero-order kinetics. The investigated formulations could be arranged according to their t50% in descending order as follows:

 M2> Thiotacid®> A1> S7> W9> D2

**Chapter III**

**Stability Study of The Selected Thioctic acid Tablets**

Depending on the previous *in-vitro* evaluation study of the prepared formulae, the tablets of formula D2 which prepared by dry granulation and contains 300mg thioctic acid, 145 mg Tablettose, 50 mg Ac-di sol and 5 mg Magnesium stearate and formula S7 which contains 300mg freeze dried thioctic acid, 50 mg Explotab, 145 mg Tablettose and 5 mg Magnesium stearate were selected for further stability study as follows:

1. **Accelerated Stability Testing**:

 The selected tablets as well as Thiotacid® tablets were stored in glass jars with plastic closures at 30º, 40º, and 50º C in oven for 12 weeks in order to clarify the predictive shelf life of the prepared tablets. Periodically, samples were withdrawn at different predetermined time intervals and examined physically for any changes, as well as chemically for their thioctic acid content using stability indicating HPLC assay. Detection of thioctic acid by the proposed HPLC method in presence of its degradation products was accomplished after initiating thioctic acid hydrolysis by the following: Two samples of the drug each one containing 40 mg; were separately dissolved in 100ml of 50% (v/v) aqueous methanol solution. The pH of the first sample was adjusted at pH 2 and the second at pH 10 using hydrochloric acid and sodium hydroxide respectively. These solutions were then placed in an oven at 50oC for three hours. 1 ml sample of each was withdrawn and completed to volume in a 10 ml volumetric flask with mobile phase and assayed for thioctic acid using the proposed HPLC assay method.

The stability indicating nature of the proposed HPLC assay was demonstrated in this study as it was capable of discriminating between the major active (intact) thioctic acid from its degradation products formed under defined storage conditions during the stability evaluation period. The chromatogram of the degraded solutions exhibited extra multiple peaks at 2.2, 3.2, 3.8, 8.8, and 11.7 minutes in addition to the drug peak appearing at 6.4 minutes.

 The unknown concentration of the drug in each tablet was calculated using the following equation:

Q = (R/A + B) x dilution factor

Where, Q is the drug concentration, R is the peak area ratio (drug/internal standard), A is the slope of the calibration curve and B is the Y-intercept.

 Accelerated stability testing results revealed that, none of the tablets stored at the three elevated temperatures for three months showed any changes in the color or the appearance throughout the storage period. The percent of drug remaining for formula D2 at 30º, 40º and 50º C for 12 weeks were found to be 98.52%, 97.63% and 96.27% respectively. While the percent remaining of the drug for formula S7 was observed to be 98.21%, 97.08% and 95.29%, at the three elevated temperatures respectively. But for the Thiotacid®, the percent of drug remained at 30º, 40º and 50º C after 12 weeks were found to be 98.24%, 96.82% and 96.11%, respectively.

 From the previous results, it is quite evident that the percent of drug decomposed from formulae stored at elevated temperature (50ºC) was higher than that stored at lower temperature (40ºC and 30 ºC).

 It is quite clear that the percent remaining of thioctic acid for all the prepared formulae at 30º, 40º and 50º C for 12 weeks was within the permitted by the USP (90%-110%) up to the end of the storage period.

 Kinetic analysis of the stability data showed that the rate of change of drug concentration was followed first-order kinetic. The data obtained at elevated temperatures were extrapolated using Arrhenious treatment and the degradation rate constant at 25°C was used for the determination of the predictive shelf life of the prepared formulae which was found to be 2.19 years for formula D2 and 1.44 years for formula S7. It is worthy to note that D2 showed the best stable results

**2-Effect of Humid Storage on Thioctic acid Prepared Tablets**

The selected thioctic acid tablets; D2 and S7 as well as Thiotacid® tablets were stored in glass dessicator at 40ºC and 75% relative humidity intiated by saturated NaCl solution, for 12 weeks. The withdrawn samples periodically after 1, 2, 6, 9 and 12 weeks were subjected to dissolution testing. The obtained results showed that the amount of the drug dissolute increased with increasing temperature and relative humidity, this may be attributed to increase the water sorbed in tablets.

**Chapter IV**

**Bioequivalence Study of the Selected Thioctic acid Tablets**

The bioavailability of the selected formulae D2 which prepared by dry granulation and contains 300mg thioctic acid, 145 mg Tablettose, 50 mg Ac-di sol and 5 mg Magnesium stearate and S7 which contains 300mg freeze dried thioctic acid, 50 mg Explotab, 145 mg Tablettose and 5 mg Magnesium stearate was determined relative to the commercially available Thiotacid® tablets containing 300 mg thioctic acid using six healthy male volunteers (weight 85-105 kg and age 26-30 years). HPLC assay was used for the determination of thioctic acid in plasma.

 Following administration of Thiotacid® tablets, the mean plasma concentration was 352.58 µg/ml (ranging from 310.36 to 419.09 µg/ml), and it was reached after 2.5 hours of drug administration. The mean AUC (0-∞) was determined and was found to be 584.93 µg.hr/ml (ranged from 579.66 to 593.49 µg.hr/ml).

While following the administration of formula S7 tablets the peak plasma concentration, Cpmax, was 390.58 µg/ml (ranging from 339.31 to 421.87 µg/ml), and it was reached after 1.5 hours of drug administration. The mean AUC (0-∞) was determined and was found to be 602.01 µg.hr/ml (ranged from 530.54 to 642.14 µg.hr/ml).

The mean peak plasma concentration was 304.88 µg/ml (ranged from 299.62 to 314.00 µg/ml), and the time of maximum plasma concentration was 2 hours after drug administration. The mean AUC (0-∞) following the administration of formula D2 tablets was found to be 567.07 µg.hr/ml (ranged from 515.99 to 620.41 µg.hr/ml).

The two-way analysis of variance (ANOVA) was performed to determine the significance of difference between the pharmacokinetic parameters of Thiotacid tablets and the prepared formulae S7 and D2. The significant level was α = 0.05; thus Cpmax and AUC (0-8) were compared for the prepared tablet formulae and Thiotacid tablets.

It was found that there was a significant difference between the peak plasma concentration and the AUC (0-8) of Thiotacid tablets and formulae D2 and S7 tablets. Also, it was clear that there was no significant difference between volunteers, indicating the absence of inter-subject variability.

The amount absorbed of the drug from the prepared tablets of formulae S7 was greater than the commercial Thiotacid® tablets as indicated by its higher AUC(0-∞) which was 602, compared to 584.3 in case of Thiotacid® tablets. Therefore the relative bioavailability of the prepared tablets of formula S7 was 102.9%. This may be due to lack of loss of drug during formulation and preparation due to its high flow properties and also may be due to the higher solubility of freeze dried thioctic acid than no treated thioctic acid.

 On the basis of the previous results formulae D2 and S7 showed good in-vitro properties, excellent stability toward the accelerated testing. The formula S7 had high relative bioavailability when compared to the commercial available Thiotacid® tablets.