ABSTRACT
Lipid-based delivery systems are becoming increasingly popular as carriers of drugs due to their ability to overcome barriers to oral absorption. The objective of the present study was to prepare novel lipid-based formulation of a sparingly soluble drug, Raloxifene hydrochloride (RLX) to increase its saturation solubility and dissolution velocity for enhancing bioavailability while reducing systemic variability. Lipid-based formulations were prepared using melted solubilization technique. The liquid formulations were converted into a solid intermediate by adsorbing onto an inert carrier and blended with excipients for encapsulation. The solid state properties, surface morphology and in-vitro release characteristics of the lipid formulations were investigated and compared with commercial formulation. The characterization of lipid formulations using Differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Scanning electron microscopy (SEM) indicated that the drug is completely enveloped in the lipid core. The dissolution characteristics of lipid based formulation filled in hard gelatin capsules showed faster rate of drug dissolution as compared to commercial tablet formulation (Fiona®). The in-vitro release studies in fed state simulated intestinal fluid (FaSSIF) and fasted state simulated intestinal fluid (FeSSIF) media indicated that, the variability in fed and fasted conditions was significantly reduced with lipid based formulation. The results from this study suggest the potential use of lipid based formulation a means of improving solubility, dissolution and concomitantly the bioavailability of a sparingly soluble drug like RLX.

KEYWORDS: Lipid based formulation, Raloxifene hydrochloride, Drug content, Powder flow properties, Food effect, Stability study.

INTRODUCTION
Oral drug delivery remains the most convenient route of administration because of its advantages over intravenous route (catheter infection; thrombosis and extravasations). However, limitations in the physical-chemical properties of the drug sometimes prevent a successful therapeutic outcome. Specifically, problems of poor solubility and chemical stability in the gastrointestinal tract, poor permeability and sensitivity to metabolism are often causes that result in the rejection of potential drug candidates as commercial products.

Over the last decade, Lipid Based Drug Delivery (LBDD) has emerged as a promising technology due to better understanding of the multiple roles of lipids that play in enhancing oral bioavailability. Moreover, the emergence of novel excipients with acceptable regulatory and safety profiles coupled with advances in formulation technologies have greatly improved the potential for successful lipid based formulations. Lipid drug delivery approach has led to the successful marketing of medicinal products including cyclosporin A (Neoral®), ritonavir (Norvir®) and saquinavir (Fortovase®). The success of these delivery systems is due to the selection of an appropriate vehicle and a rational delivery system design.

A lipid-based oral formulation is used for water-insoluble drugs in cases where typical formulation approaches (i.e., solid wet granulation, solid dry granulation, water-soluble liquid in a capsule) fail to provide the required bioavailability, or when the drug itself is an oil (i.e., dronabinol, ethyl icosapentate, indometacin farnesil, teprenone, and tocopherol nicotinate). In practice, lipid formulations are a diverse group of formulations, which result from the blending of excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and water-soluble co-solvents. Depending on the choice of excipient(s) and formulation techniques, it is possible to obtain a variety of systems including physical mixtures, liquid/solid solutions, solid dispersions, and Self-Micro or Self-Nano Emulsifying Drug Delivery Systems (SMEDDS/SNEDDS). These systems may then be incorporated into capsules directly, or transformed into granules, pellets, and powders for filling into capsules as well as tablet preparations.

The use of lipid based drug formulations that enhance the bioavailability of poorly water-soluble drugs has gained interest, because they utilize the well-known food effect of the ingested lipids. Lipid based formulations can reduce slow and incomplete dissolution by facilitating the formation of solubilized phases and, if very lipophilic, increase the amount of drug transported via the intestinal lymphatic system, thereby increasing absorption from the gastrointestinal tract. Although the exact mechanisms responsible for enhanced absorption are not fully known, possible mechanisms of intestinal drug absorption, using lipid-based formulations, are summarized in Figure 1. These mechanisms include, an increase in membrane fluidity facilitating transcellular absorption (Figure 1-[I]), opening of the tight junction (TJ) to allow paracellular transport, mainly relevant for ionized drugs or hydrophilic macromolecules (Figure 1-[II]), inhibition of P-gp and/or CYP450 to increase intracellular concentration and residence time (Figure 1-[III]), and stimulation of lipoprotein / chylomicron production (Figure 1-[IV]) may make significant contributions. The latter two mechanisms are potentially the most promising for intestinal lymphatic drug targeting using lipid-based vehicles.

In the present study, an attempt was made to enhance the solubility and in vitro dissolution of RLX by formulating it as lipid based formulation for filling into hard gelatin capsules. RLX is a relatively new selective estrogen receptor modulator (SERM), and its chemical structure is depicted in Figure 2. It acts as an estrogen agonist on bone and on the liver and therefore increases bone mineral density and decreases fracture incidence. It is used in the prevention of

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osteoporosis and prevention of invasive breast cancer in postmenopausal women. The major issue that has limited the therapeutic efficacy of RLX as an oral dosage form is its low solubility in physiological pH conditions and extensive first pass metabolism. RLX exhibits high inter-individual and intra-individual variability (30%) of most pharmacokinetic parameters. Clinical studies revealed that the absolute bioavailability of RLX in humans is 2%. The main objective of this study was to improve the bioavailability and minimize variability of RLX by preparing lipid based drug delivery system. The formulation was characterized for its solubility, drug release profile, food effect and stability criteria.

MATERIALS & METHODS

Materials

Raloxifene HCl (RLX) was procured from Dr. Reddy’s Laboratories Ltd., Hyderabad, India. Phospholipids (Soy Phosphatidylcholine, Dimyristoyl phosphatidylcholine (DMPC), Dipalmitoyl phosphatidylglycerol (DPPG), Egg phosphatidylcholine and Cholesterol) were obtained from Avanti polar lipids, USA. Labrasol® (Caprylocaproyl macrogol-8 glycerides) was obtained from Gattefosse, France. Tween-80® (Polyoxethylene (20) sorbitan mono oleic acid) was obtained from Merck Specialities, Mumbai. Aerosil® 200 pharma was obtained from Evonik Degussa GmbH, Germany. Propylene glycol was obtained from Fischer scientific (Fair lawn, NJ, USA). Soya Lecithin was obtained from Himedia laboratories, Mumbai. Taurocholic acid sodium salt was obtained from Sigma Aldrich, USA.

METHODS

Exciplent Screening – Solubility Studies

The excipients used in the formulation were selected based on their ability to enhance the solubility of drug in water. Similarly, the solubility studies were carried out for each of them. The effect of phospholipids on the solubility of the drug in water was investigated using the Rotary shaking method. For this, certain amount of Phospholipids was added to 20 mL of water in a stoppered conical flask. To this excess amount of water was added and agitated continuously in a Rotary shaker for 48 Hrs, 200 rpm at 25° C and 37° C, till saturation was observed. The obtained samples were filtered using 0.45 µm syringe filters and analyzed using HPLC at 287 nm. In order to estimate the effect of excipients on the solubility of drug, a specific amount of the excipient was taken equivalent to certain ratio of the drug. For this, the required ratio of drug: phospholipids: excipient was added to 10 mL of water in a stoppered conical flask and was carried out for rotary shaking and samples were estimated as described earlier.

Design of Lipid Based Formulation

Based on the solubility data, different excipients (phospholipids, solvent, surfactant and co-surfactant) were evaluated to develop a viable formulation. The selection and optimization was done based on the dissolution enhancement ability of the excipients used at different stages of formulation development. A series of four formulations were prepared by varying the concentrations of solvent, surfactant, co-surfactant and solid carrier. In all the formulations, the level of RLX was kept constant (i.e. 60 mg). Required amount of propylene glycol was taken in a glass vial and heated to around 60°C. To this accurately weighed amount of RLX was added and stirred to dissolve completely. Phospholipids, surfactant and co-surfactant were added and stirred continuously to obtain a clear solution of drug in lipids. The formulations were stored at room temperature until further use.

Conversion to Solid Intermediates of Lipid Based Formulation

The liquid lipid based formulation was converted into free flowing powder by adsorbing of liquid formulation onto solid carrier. The solid carrier used for adsorption comprised of materials that provided a high surface area with good disintegration characteristics. The solid carrier used included Aerosil 200® pharma (high purity amorphous and anhydrous grade of colloidal silicon dioxide). The conversion process involved addition of liquid formulation onto carrier under continuous mixing in a blender. The powder was dried and filled directly into capsules or alternately blended with suitable excipients for tabletting.

Characterization of Solid Lipid Based Formulation of Raloxifene Hydrochloride

Drug Content (%)

The drug content was estimated by dropping 4 capsules in a 1000 mL volumetric flask. Diluent was added to the flask to dissolve the drug under Sonication for 10 min. The solution was filtered through 0.45µm syringe filters. From the filtrate, 1 mL was transferred into a 25 mL volumetric flask which was diluted and made up to volume with the diluent. This solution was used for analyzing the drug content using HPLC.

\[
\text{Drug Content (mg/Cap)} = \frac{A_t}{A_w} \times 100\%
\]

Where,

- \(A_t\) = peak area of RLX in the sample preparation.
- \(A_w\) = peak area of RLX in the standard preparation.
- \(S_w\) = weight of RLX working standard taken in mg.
- \(T_w\) = weight of sample taken in mg.
- \(P\) = potency (%) of RLX working standard calculated as API.
- \(Avg. wt\) = Average weight of the capsule taken in mg.
- \(L\) = label Claim of RLX working standard calculated as API.

HPLC Analysis

The analysis was carried out using Waters Alliance High-performance liquid chromatography system (Agilent Technologies, USA). Chromatographic separation was accomplished using a Zodiac sil 300-5-C4, 150x4.6 mm, 5µ stainless steel column (Agilent Technologies, USA). The mobile phase consisted of a mixture of buffer (50 mM monobasic potassium phosphate) and acetonitrile in the ratio of 64.36 (% v/v), with pH of the buffer being adjusted to 3.0 using ortho phosphoric acid. The mobile phase was pumped isocratically at a flow rate of 0.7 ml/min during analysis, and the column temperature was maintained at 37°C. The amount of drug dissolved at each sampling time point was estimated using a UV wavelength of 287 nm.

Powder Flow Properties

Angle of Repose (θ)

The funnel method was used to evaluate the flow properties of solid lipid formulation (granules). In this method a sufficient quantity of granules were poured in to a funnel (initially closed at the tip). The height of the tip was kept at distance of 2 cm from the bottom of the surface and the granules were allowed to flow through the orifice, to form a heap on the surface. A rough circle was drawn around the heap base and the diameter of the heap was measured (D). The angle of repose was calculated using the following formulae.
Tan $\theta = H / R$

Where,
$\theta$ = Angle of repose
$H$ = Height of the tip from surface
$R$ = Radius of the heap (D/2)

**Bulk Density**

It was measured by a pouring the known mass of granules (M) into a measuring cylinder. Then initial volume was noted and was called as bulk volume ($V_b$). From this, bulk density was calculated using the following formulae.

$$\rho_b = M / V_b$$

Where,
$\rho_b$ = Bulk Density
$M$ = Weight of sample in gm
$V_b$ = Initial untapped volume of granules in cm$^3$

**Tapped Density**

The measuring cylinder containing a known mass of granules (M) was tapped for 500 taps in Tapping apparatus. The volume of the granules after tapping was measured ($V_t$). The tapped density was calculated using the following formulae.

$$\rho_t = M / V_t$$

Where,
$\rho_t$ = Tapped Density
$V_t$ = Final tapped volume of granules in cm$^3$

**Carr’s Compressibility Index**

It gives the flow property of the granules. Compressibility index of less than 25% indicates good flow property. It was calculated using the following formulae,

$$CI = \left( \frac{\rho_b - \rho_t}{\rho_b} \right) \times 100$$

**Hausner Ratio**

It is used for flow property of the granules. A Hausner ratio of less than 1.25 indicates better flow property. It was calculated using the following formulae.

$$HR = \frac{\rho_t}{\rho_b}$$

**In-Vitro Release Studies**

The release of drug from liquid formulations, solid intermediates filled in capsules, and commercially available tablet formulation (Fiona®) was determined using a USP type II dissolution apparatus. Initially for the optimization of the formula, the in vitro release was investigated in discriminating dissolution conditions, which included 500 mL of purified water as discriminating media being maintained at 37°C with the paddle operated at 50 rpm and non-sink conditions. An aliquot of 10 ml was withdrawn at predetermined intervals 15, 30, 45, and 60 min and filtered through 0.45 μm pore size membrane filters (Zodiac Life sciences, India). The amount of drug dissolved was determined using an HPLC method as described earlier.

**Solid State Characterization of Solid Lipid Based Formulation**

The solid state properties of RLX in the solid lipid based formulation (optimized) was investigated using Differential Scanning Calorimetry (DSC) and X-Ray powder Diffraction (XRPD), since this would influence the in vitro and in vivo characteristics.

**Differential Scanning Calorimetry (DSC)**

Thermal properties of drug, placebo and granulated lipid formulation were investigated using DSC Q-1000 (TA Instruments, USA). Weighed samples of 3 – 5 mg were taken in an open aluminum DSC pans and then sealed and crimped. These samples were scanned at a ramp of 10°C/min over a range of 10 – 300 °C under an inert environment using Nitrogen.

**X-Ray Powder Diffraction (XRPD)**

XRPD diffractograms of drug, placebo, and granulated lipid based formulations were recorded using a Panalytical Xpert Pro Diffraactometer (PANalytical, Netherlands) with a Cu line as the source of radiation. Standard runs using a 40-kV voltage, a 40-mA current, and a scanning rate of 0.02° min⁻¹ over a 2θ range of 3–40° were used.

**Morphological Analysis of Solid lipid Based Formulation**

Scanning Electron Microscopy (SEM)

The surface morphology of the solid lipid formulation was investigated by scanning electron microscope (Hitachi S 3000 N), operating at 10 KV. Few mg of sample was taken on the aluminum stub, present on the specimen holder. An adhesive was used to attach the sample to the stub. Further, the stub along with the sample was placed in the Hitachi vacuum evaporator (HUSGB) and was sputter coated with gold. This coated sample was placed in the chamber of SEM instrument for analysis. An accelerated voltage of 10 KV and a vacuum of less than 1 Pascal were used during the SEM analysis. Photographs were taken for each of the sample.

**Assessment of Food Effect**

Biorelevant media can provide a more accurate simulation of pharmacokinetic profiles than simulated gastric fluid or simulated intestinal fluid. Similarly, according to the literature¹, biorelevant media were prepared. The dissolution was carried out in recommended volume of FeSSIF (1000 mL) / FaSSIF (500 mL) media at 37°C and paddle type with 50 rpm speed along with the maintenance of sink conditions. For this, each capsule was dropped in the dissolution apparatus with the help of a sinker. At pre determined time intervals, aliquots of sample (10 mL) was withdrawn and filtered through 0.45μm syringe filters. The filtered samples were diluted accordingly and analyzed at 287 nm using HPLC method. The cumulative % drug dissolved was calculated at each interval. A graph containing cumulative % drug dissolved on Y-axis and Time on X-axis was plotted and comparison was done between the lipid formulation and marketed product (Fiona®).

**Stability Study**

The optimized formulations were subjected to stability studies for a period of three months in accelerated and real time conditions. The filled capsules were packed in HDPE bottles and charged for stability studies at 25°C / 60 % RH and 40°C / 75 % RH. At predetermined time intervals of 15, 30, 60 and 90 days, the samples were analyzed for the drug content (%) and the in vitro dissolution studies. The dissolution of the lipid formulations and marketed product were carried out in release medium (900mL of 0.001 N HCl (pH-3.0), 75 rpm and 37°C).

**RESULTS AND DISCUSSION**

**Excipient Screening – Solubility Studies**

The solubility results carried out with phospholipids and other excipients were summarized in Table 1 and 2. The drug substance showed good solubility in Tween 80, Labrasol and Propylene glycol. Among the phospholipids, Soy PC and DMPC showed the desired solubility for dosage development.

Solubility of drug substance in lipid carriers is a key criterion for selection of components for developing a lipid based formulation. Based on the drug’s solubility and compatibility with hard gelatin capsule shell, Propylene glycol was selected as solvent, Labrasol was selected as surfactant and Tween 80 was selected as co-surfactant for further development. The components selected are miscible with each other and form a homogenous mixture. It is well established that medium
chain fatty acids influence the tight junctions of the epithelial cells and long chain fatty acids stimulate the lipoprotein synthesis and subsequent lymphatic absorption and thus enhancing drug bioavailability.

**Design of Lipid Based Formulation**
The solid lipid based formulations were prepared by melt solubilization followed by adsorption technique. The varying concentrations of excipients, in the lipid based formulations are summarized in Table 3. The formulation showing maximum drug release, highest drug content and good flow properties was selected (optimized) for further study.

**Characterization of Solid Lipid Based Formulation of Raloxifene Hydrochloride**

**Drug Content (%)**
The result of drug content (%) for solid lipid based formulations is summarized in Table 4. The Lipid formulation D having 4:1 ratio of Liquid lipid formulation: Aerosil® 200 Pharma showed highest drug content i.e. 99.9%, and was carried out for further study.

**Powder Flow Properties**
The granules (lipid based solid intermediate) were evaluated for its flow properties and the results are indicated in Table 5. Their bulk and tapped densities were estimated and the Angle of repose, Carr’s compressibility index and Hausner ratio were calculated. Lipid formulation D with 4:1 ratio of Liquid lipid formulation: Aerosil® 200 showed good flow properties, while that of Lipid formulation B with 5:1 ratio showed poor flow property.

**In Vitro Release Studies**
The comparative in vitro dissolution data of lipid based formulations in discriminating dissolution medium (500 mL of water, non-sink conditions) is depicted in Figure 3. The data indicated significantly higher drug dissolution from solid lipid based formulations when compared to liquid and marketed formulation (Fiona®). The faster dissolution from lipid based formulation may be attributed to the fact that, in this formulation, the drug is in solubilized form and upon exposure to dissolution medium, results in small droplets that can dissolve rapidly in the dissolution medium. Formula composition of the selected (optimized) solid lipid based formulation is shown in Table 6. The drug dissolution from solid intermediates in capsules was comparable and significantly higher than the liquid formulation and commercial tablet as depicted in Figure 4. The higher drug release in case of solid formulation, when compared to liquid formulation may be attributed to the use of solid carrier (Aerosil 200® pharma) with high BET surface area, which improved the solubilization of the drug. Based on the results, Lipid formulation D was selected as the optimized formulation for further characterization. The similarity factor (F2) calculated on the dissolution data of marketed formulation and solid lipid based formulation is 27, which indicated that the marketed formulation is dissimilar to solid lipid based formulation.

**Solid State Characterization of Solid Lipid Based Formulation**

**Differential Scanning Calorimetry (DSC)**
The DSC thermograms of pure drug, placebo, and granulated lipid formulation (optimized) are shown in Figure 5. Pure drug substance showed sharp endothermic peaks at 267.58°C indicating that the drug is highly crystalline. The absence of drug peaks in the granulated lipid formulation indicates change in the melting behavior of drug and inhibition of crystallization following granulation using lipid surfactants and granulating materials.

**X-Ray Powder Diffraction (XRD)**
The X-ray diffractograms of pure drug, placebo, and granulated lipid formulation (optimized) are shown in Figure 6. The results depicted an absence of obvious peaks representing crystals of RLX in granulated lipid formulation indicating that the drug was in amorphous or disordered crystalline phase in the lipid matrix.

**Morphological Analysis of Solid Lipid Based Formulation**

**Scanning Electron Microscopy (SEM)**
The SEM images of pure drug, placebo, and granulated lipid formulation (optimized) are shown in Figure 7. The SEM images of granulated lipid formulation show well-separated particles with no agglomeration.

**Assessment of Food Effect**
The dissolution profile shown in Figure 8 indicated the effect of food (fatty meal) on the dissolution rate of RLX. Comparing the release rate of drug in fed and fasted state simulated intestinal fluid, RLX exhibited a significant food effect from the marketed product (Fiona®), while the food effect was insignificant from the lipid based formulation (D). This might be attributed to the reduction of slow and incomplete dissolution, by facilitating the formation of solubilized phases, due to the presence of lipids in the formulation itself, which helped the dissolution of drug to the same extent in both fed and fasted conditions, irrespective of the lipids present in the fed state simulated medium. Hence, the difference in the dissolution and bioavailability of a lipophilic, poorly water soluble compound found in fed compared to fasted state can be circumvented by using a lipid or surfactant based formulation.

**Stability Study**
The stability profiles of the selected lipid based formulation and the marketed formulation (Fiona®) is depicted in Figure 9. During the three months of stability study, none of the stored samples of lipid based formulation showed any change in color or appearance under all storage conditions. There was no significant difference in RLX content and dissolution profiles of lipid based formulation at zero time and through the three month stability study period under all storage conditions. This indicates that RLX did not degrade or precipitate which infers the stability of lipid based formulation and its release properties.

**CONCLUSION**
A solid lipid based formulation of a poorly water-soluble drug, Raloxifene HCl was formulated for direct filling into hard gelatin capsules for oral administration. The lipid formulation showed faster rate of drug release than the marketed product in a discriminating dissolution media. From the in vitro dissolution and solid state characterization data it is apparent that the presence of Soy PC, DMPC and Labrasol® together as solubilizers and carriers has a significant impact on dissolution characteristics. The dissolution profiles in the fed and fasted state simulated intestinal fluid showed a very insignificant effect or almost negligible effect of food on the dissolution rate of RLX from the lipid based formulation. On charging the optimized formulation to accelerated stability studies for a period of three months, it was noticed that, there was neither drug precipitation nor a reduction in the release rate of RLX from the lipid based formulation indicating good stability of the formulation. Thus the prepared lipid based formulation proved to be a potential technology for enhancing the transfer of poorly water soluble lipophilic compounds to the aqueous phase, thus enhancing the bioavailability, which may result in improved therapeutic performance.
REFERENCES

TABLE 1: SOLUBILITY OF DRUG IN PHOSPHOLIPIDS

<table>
<thead>
<tr>
<th>Medium</th>
<th>Solubility (mg/mL)</th>
<th>At 25°C</th>
<th>At 37°C</th>
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<tr>
<td>Cholesterol</td>
<td>0.446±0.15</td>
<td>0.545±0.14</td>
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<td>Soy PC</td>
<td>0.560±0.11</td>
<td>0.627±0.10</td>
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<tr>
<td>DMPC</td>
<td>0.591±0.10</td>
<td>0.612±0.15</td>
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<tr>
<td>DPPG</td>
<td>0.183±0.09</td>
<td>0.181±0.08</td>
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TABLE 2: SOLUBILITY DATA OF VARIOUS FORMULA COMPOSITIONS

<table>
<thead>
<tr>
<th>Drug (mg)</th>
<th>Soy PC (mg)</th>
<th>DMPC (mg)</th>
<th>Labrasol® (mg)</th>
<th>Propylene glycol (mg)</th>
<th>Tween-80 (mg)</th>
<th>Solubility (mg/mL)</th>
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<tbody>
<tr>
<td>30</td>
<td>30</td>
<td>30</td>
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<td>30</td>
<td>60</td>
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<td>60</td>
<td>-</td>
<td>0.8311±0.11</td>
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<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>-</td>
<td>15</td>
<td>0.9953±0.13</td>
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TABLE 3: OPTIMIZED CONCENTRATIONS OF SOLVENT AND SURFACTANT

<table>
<thead>
<tr>
<th>Lipid Formulation</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
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</thead>
<tbody>
<tr>
<td>Drug</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Soy PC</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
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<tr>
<td>DMPC</td>
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<td>60</td>
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<td>Labrasol®</td>
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<td>120</td>
<td>120</td>
<td>60</td>
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<td>Propylene Glycol®</td>
<td>-</td>
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<td>150</td>
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<td>Tween-80</td>
<td>-</td>
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<td>180</td>
<td>90</td>
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<tr>
<td>Aerosil® 200 Pharma</td>
<td>60</td>
<td>180</td>
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<td>120</td>
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TABLE 4: PERCENTAGE DRUG CONTENT OF THE CAPSULE DOSAGE FORM

<table>
<thead>
<tr>
<th>Lipid Formulation</th>
<th>Drug Content (%)</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>98.7±1.12</td>
</tr>
<tr>
<td>B</td>
<td>95.5±1.35</td>
</tr>
<tr>
<td>C</td>
<td>98.8±1.02</td>
</tr>
<tr>
<td>D</td>
<td>99.9±0.92</td>
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TABLE 5: FLOW PROPERTIES OF THE GRANULES

<table>
<thead>
<tr>
<th>Lipid Formulation</th>
<th>Angle of Repose (θ)</th>
<th>Bulk Density (g/mL)</th>
<th>Tapped Density (g/mL)</th>
<th>Carr's Compressibility Index (%)</th>
<th>Hausner Ratio</th>
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<tbody>
<tr>
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<td>23.4</td>
<td>0.416</td>
<td>0.500</td>
<td>16.80</td>
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<td>B</td>
<td>34.7</td>
<td>0.405</td>
<td>0.555</td>
<td>27.02</td>
<td>1.37</td>
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<tr>
<td>C</td>
<td>25.6</td>
<td>0.365</td>
<td>0.454</td>
<td>19.60</td>
<td>1.24</td>
</tr>
<tr>
<td>D</td>
<td>22.2</td>
<td>0.394</td>
<td>0.468</td>
<td>13.81</td>
<td>1.18</td>
</tr>
</tbody>
</table>

TABLE 6: OPTIMIZED FORMULA FOR RLX LIPID BASED FORMULATION

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Weights (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>60</td>
</tr>
<tr>
<td>Soy PC</td>
<td>60</td>
</tr>
<tr>
<td>DMPC</td>
<td>60</td>
</tr>
<tr>
<td>Labrasol®</td>
<td>60</td>
</tr>
<tr>
<td>Propylene Glycol</td>
<td>150</td>
</tr>
<tr>
<td>Tween-80</td>
<td>90</td>
</tr>
<tr>
<td>Aerosil® 200 Pharma</td>
<td>120</td>
</tr>
<tr>
<td>Total wt.</td>
<td>600</td>
</tr>
</tbody>
</table>
Figure 1: Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations.

Figure 2: Structure of raloxifene hydrochloride

Figure 3: Comparative dissolution profiles of lipid based formulations in discriminating dissolution conditions

Figure 4: Comparative dissolution profiles between pure drug, marketed formulation (Fiona®), liquid and solid lipid based formulation
Figure 5: Thermograms of pure drug (API), placebo and granulated lipid formulation.

Figure 6: X-Ray Diffraction patterns of pure drug (API), placebo and granulated lipid formulation

Figure 7: SEM images of pure drug (left), Placebo Lipid Formulation (middle), Granulated Lipid Formulation (right)

Figure 8: Comparative dissolution profiles of marketed formulation (Fiona®) and RLX in biorelevant media
Figure 9: Comparative stability results

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