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In-vitro Release and Stability Studies of Raloxifene Loaded Solid-Lipid Nanoparticle

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Objective: Raloxifene HCl (RLX) show a low oral bioavailability (<2%) in human due to its poor solubility and extensive (>90%) first-pass metabolism. To overcome these limitations, the present investigation deals with the development of Compritol 888 ATO based optimized RLX-loaded solid lipid nanoparticle (SLN) .
Methods: Compritol 888 ATO-based RLX-loaded optimized solid lipid nanoparticle (SLN) were formulated using oil in water microemulsion method. Drug-excipients compatibility was confirmed through a powder X-ray diffraction study. The optimized SLN was characterized for particle size and drug release.
Results: Drug-excipients compatibility was confirmed powder X-ray diffraction study. As per the desirability function value (0.959) the optimized formulation has the size and EE of 168.97 nm and 93.14%. *In-vitro* study showed a sustained release of RLX from the optimized SLNs. The optimized formulation was found stable for 180 days.
Conclusion: The high biocompatibility, biodegradability, ability to protect drug in GIT and sustained release properties make SLNs an ideal candidate to resolve poor oral bioavailability challenges.

Keywords: Nanoparticles; drug delivery; raloxifene; solid-lipid nanoparticle; drug release.

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1. INTRODUCTION

Raloxifene hydrochloride (RLX) is a second-generation selective estrogen receptor modulator (SERM) that has anti-estrogenic effects on breast and uterine tissues, and estrogenic effects on bone, lipid metabolism, and blood coagulation [1]. It is considered first-line therapy for the management of postmenopausal osteoporosis [2]. Poor solubility of the RLX (0.25mg/lit) results in only 60% absorption of the administered dose and poor oral bioavailability (less than 2%). In addition, extensive first-pass metabolism of RLX by glucuronide conjugation also results in its poor oral bioavailability [3]. The RLX comes under class II (low solubility and high permeability) of biopharmaceutical classification [4]. The poor water solubility and poor oral bioavailability present a continuous challenge for the formulation development and effective treatment of the diseases. Therefore there is an unmet need for an effective delivery system that can overcome the existing challenges.

To date, solid-lipid nanoparticles (SLNs) have emerged as potential carriers that can enhance the solubility and oral bioavailability of poorly water-soluble drugs [5]. SLNs have a lipid core that mimics the chylomicrons formation and along with the loaded drug it absorbs through the transcellular mechanism of lipid absorption [6]. In addition to their small size, the SLNs have combined property of a lipid emulsion and the polymeric nanoparticle with enhanced biocompatibility, biodegradability, ability to protect drug in the gastrointestinal tract (GIT) from the harsh environment, sustained drug release, and rapid uptake [7]. Studies have shown that the RLX loaded into the triglyceride-based SLNs has improved oral bioavailability compared to a free RLX [8]. However, studies have shown that the SLNs prepared with triglycerides with shorter carbon chain length have some limitations for oral administration due to their susceptibility towards intestinal lipase and co-lipase enzyme system [9]. However, SLNs prepared with lipids having a higher carbon chain, such as Compritol 888 ATO (glyceryl behenate) are more resistant to the enzyme system. Moreover, SLNs prepared with stabilizers, such as poloxamers have longer circulation duration in the body reduced protein adsorption, and low phagocytic uptake [10].

In the present investigation, we used the Box–Behnken design (BBD) for the optimization of RLX-loaded SLN. We have investigated the drug-excipients compatibility by powder X-ray diffraction techniques (PXRD). The model used for the optimization was analyzed statistically via ANOVA and the goodness of fit was evaluated through different diagnostic plots. The optimized condition was selected based on the desirability function value and the fresh formulation was developed to validate the optimized set parameters. Finally, the optimized formulation of raloxifene was evaluated for in-vitro drug release and stability in a set condition for 180 days.

2. MATERIALS AND METHODS

2.1 Materials

Raloxifene hydrochloride was obtained as a gift sample from Archerchem Healthcare Pvt India. Poloxamer 407 was purchased from SD fine chemicals, Mumbai, India India. Compritol 888 ATO was obtained as a gift sample from Archerchem Healthcare Pvt India. Dimethyl sulfoxide (DMSO) was purchased from SD fine chemicals, Mumbai, India. All other chemicals are of analytical grade.

2.2 Drug-excipients Compatibility Studies

2.2.1 Powder x-ray diffractometry

Powder X-ray diffractometric (PXRD) pattern of RLX and Physical mixture was obtained by employing X-ray diffractometer (Bruker, D 8-Advance,Japan); Ni-filtered Cu-K radiation, the voltage of 40 kV, and current of 30mA radiation scattered in the crystalline regions were used and measured with a vertical goniometer. Patterns were obtained by using a step size of 0.045ºC with a detector resolution in 2θ (diffraction angle) between 5º and 80º at 25ºC temperature.

2.3 Optimization and Desirability Function

The effect of variables (A: Lipid, B: P407 and C: Sonication time) on the particle %EE was evaluated using contour (2D) and Response-surface (3D) plots. Contour and response-surface plots between lipid and P407, keeping sonication time constant showed an increase in %EE with increase in amount of lipid. Contour and response-surface plots between the sonication time and lipid keeping P407 constant showed a significant increase in %EE with increase in lipid amount. The sonication time has

no signinificant effect on the %EE .Contour and response-surface plots between the sonication time and P407 showed an increase in %EE with increase in P407 concentration. The sonication time has no signinificant effect on the %EE.

The desirability function was analyzed to generate an optimized formulation composition, which was obtained using the set predetermined desired quality of the final product, such as minimum size and maximum %EE.

The calculated desirability factor for offered formulations was 0.959, indicating suitability of the designed factorial model. The results of dependent variables from the software were found to be 93.14% for %EE and -168.97nm size at these levels. (Fig. 1). This proved that the derived contour plots could be useful in the preparation of RLX-loaded SLNs of predetermined %EE and particle size.

2.4 *In-vitro* Drug Release

The *In-vitro* drug release studies of the optimized RLX-loaded SLNs were performed according to the method described in the previous study [11,12]. Briefly, release studies were performed using pH 6.4 phosphate buffer containing Tween 80 (0.5% v/v) by dialysis bag method using dialysis membrane having a molecular weight of 12,000–14,000 daltons. An SLN dispersion equivalent to 10 mg of drug was filled into a dialysis bag tied in both the end and placed inside the beaker (50 ml) filled with diffusion medium. The setup was maintained at 37 ±2ºC with continuous stirring at 100 rpm using a magnetic stirrer. At the predetermined time intervals (0, 1, 2, 4, 6, 8, 10, 24, 48, and 72 hr), the sample (3 ml) was withdrawn and the same volume of fresh medium was replaced to maintain the sink condition. The samples were analyzed at 286 nm using a UV-vis spectrophotometer.

2.5 Stability Study

The stability studies of the optimized RLX-loaded SLN formulation were performed by being stored in sealed glass vials at 32±2ºC for 180 days and were examined at regular time intervals for changes in particle size and % EE.

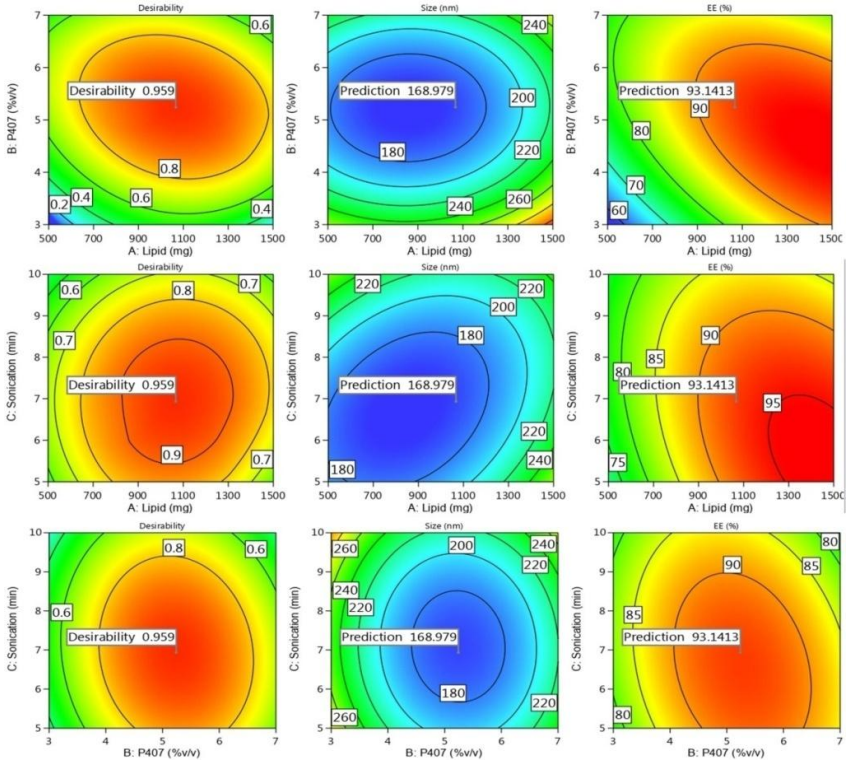

Fig. 1. Contour plots showing desirability value and desired properties of the SLN with different optimized variables combinations

3. RESULTS AND DISCUSSION

3.1 Drug Excipients Compatibility

The drug-excipients compatibility was evaluated using XRD. According to the XRD results, the pure RLX drug showed distinct peaks at 2θ of 12.812^o, 14.47^o, 15.784^o, 19.153^o, 22.682^o, and 25.876^o(Fig. 2 (A)).

All these peaks are also visible in the physical mixtures Fig. 2 (B and C). The result indicates the drug-excipient's compatibility and their suitability for the formulation development.

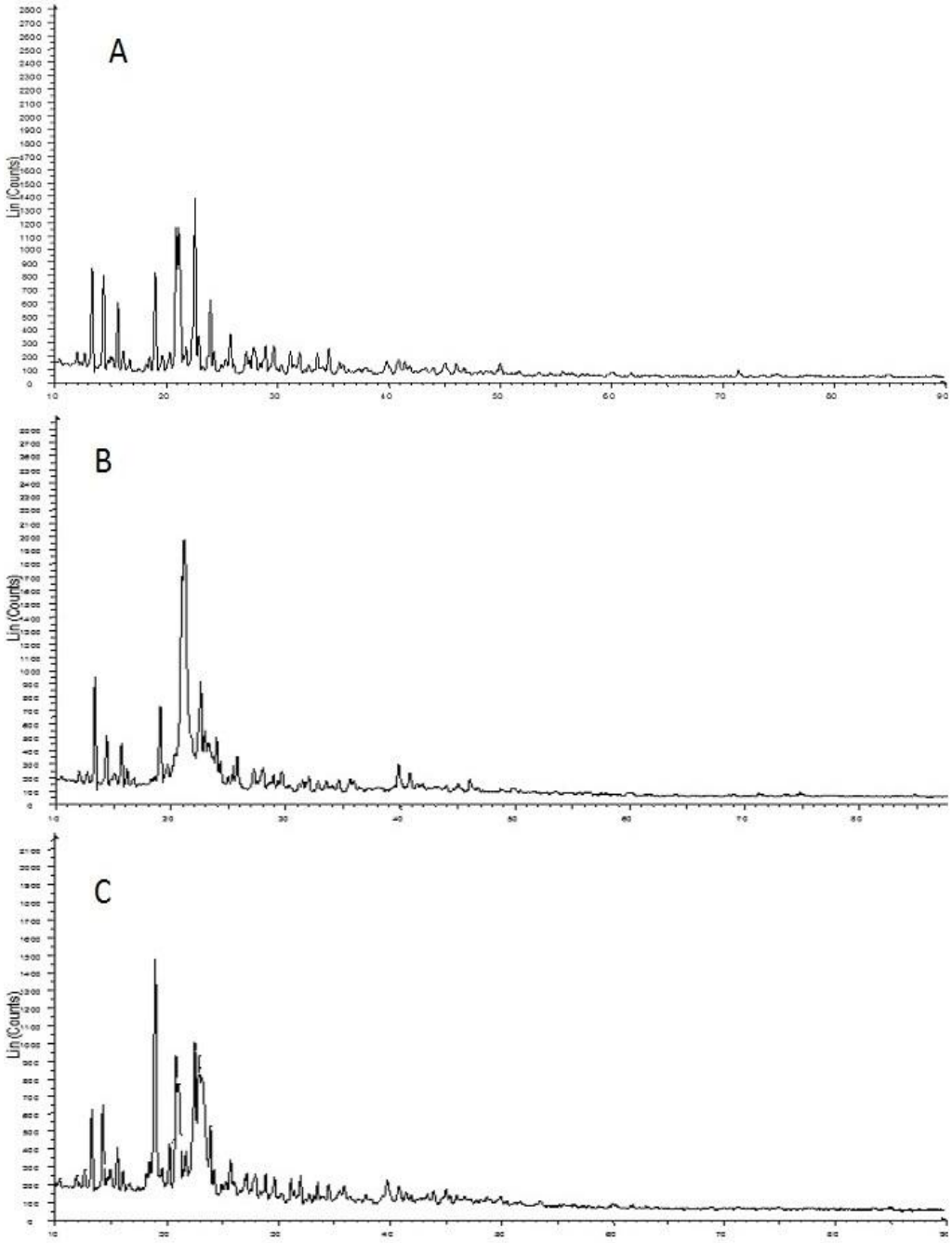

Fig. 2. PXRD graphs of (A) RLX, (B) RLX+ RLX+ Compritol 888 ATO and (C) RLX+P407

3.2 Optimized Formulation and Drug Release

Depending upon the optimized combination obtained from the QbD design, a fresh batch of RLX-loaded SLNs was developed to validate the outcome. The freshly prepared nanoformulation has a size of 169.32 nm and %EE of 92.85%. Drug release of RLX-loaded SLNs was compared with that of pure RLX (Fig. 3(B)). Free RLX was completely dissolved within 4 hr. However, the RLX-loaded SLNs showed a typical biphasic drug release pattern. An initial rapid release (burst release) within the first 1-2 hrs followed by a slow-release phase for up to 72 hr. The initial rapid release of the drug was due to the RLX present on the surface of the particle. In addition, the P407 which covers the surface of the SLNs can also entrap some of the drugs released at the initial time point. After this, the drug diffused slowly from the lipid matrix (Fig. 3 (B)).

3.3 Stability Study

Stability estimation for optimized RLX-loaded SLN formulation was done on basis of particle size and %EE variations during 180 days study period. The optimized formulation was found quite stable with a slight change in particle size and %EE (Fig. 4).

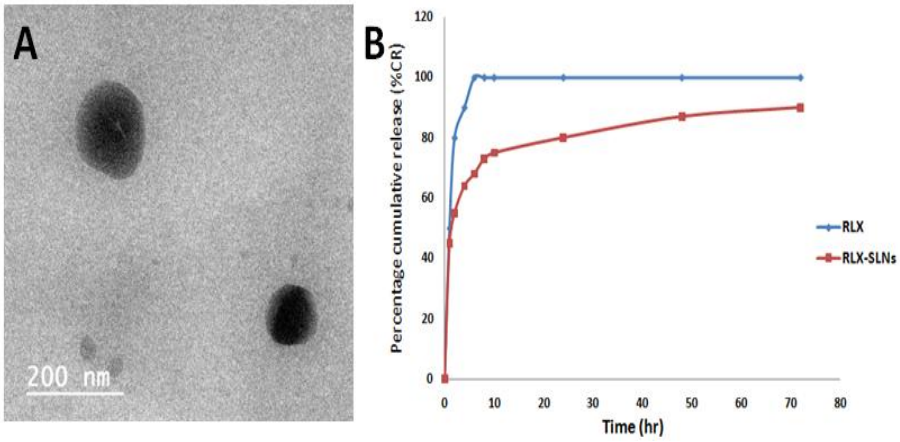

Fig. 3. *In vitro* drug release profile for RLX-SLNs and free drug

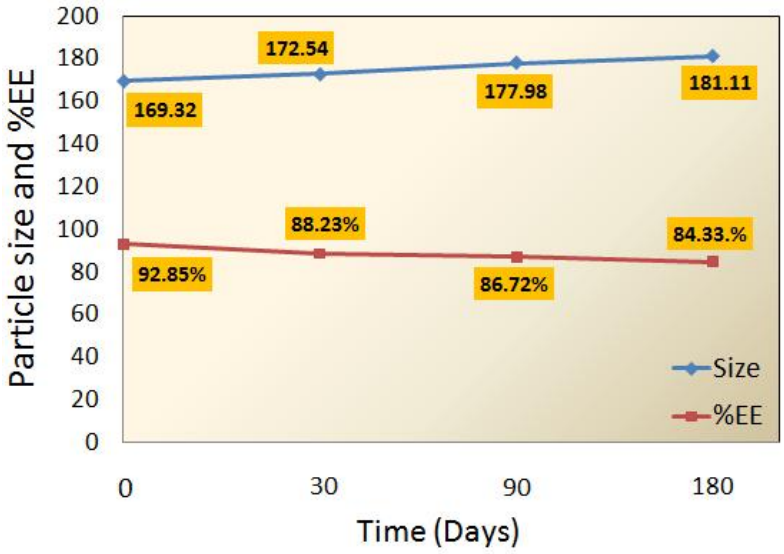

Fig. 4. Effect of storage on the particle size and %EE of the optimized RLX-loaded SLN

4. CONCLUSION

The poor water solubility of the drug not only affects its oral bioavailability but also therapeutic effects, however, it presents a great challenge for formulation development. In form past decade, SLNs have emerged as a potential delivery system that can effectively overcome these limitations. SLNs becomes an ideal candidate to resolve poor oral bioavailability challenge due to its high biocompatibility, biodegradability, ability to protect drug in GIT and sustained release properties. In the present investigation, Compritol 888 ATO-based optimized SLN was successfully prepared via emulsion technique. The formulations were optimized via the desirability function which gives a set of conditions for the development of SLN with desired properties. Finally, the optimization values were validated through formulating the optimized formulation and evaluated for release *in-vitro*. Finally, the developed RLX-loaded SLN were found stable. To conclude, SLN of RLX could be an effective strategy in reducing the dose of the drug and enhancing its oral bioavailability.

DISCLAIMER

The company name used for this research is commonly and predominantly selected in our area of research and country. There is absolutely no conflict of interest between the authors and company because we do not intend to use this company as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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