Available online on 15.07.2021 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Formulation and Evaluation of Self Nano Emulsifying Drug Delivery System of Raloxifene Hydrochloride

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Article Info:

Article History:

Received 08 May 2021
Review Completed 19 June 2021
Accepted 24 June 2021
Available online 15 July 2021

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Abstract

Raloxifene hydrochloride (RLX) is a selective Estrogen-receptor modulator used to treat osteoporosis as well as breast and endometrial cancer prevention. The bioavailability of RLX is only 2% due to substantial pre-systemic clearance. The goal of this research was to customise and characterise RLX-loaded self-nanoemulsifying drug-delivery systems (SNEDDS) by using bioactive excipients that impact drug metabolism. The droplet size, zeta potential and drug content determination of optimized formulation (F-06) was found to be 147.5 nm, -28.8, 99.67% respectively. The drug release study from the nano formulation was studied in Phosphate buffer 6.8 for all the formulations F1,F2,F3,F4,F5,F6 and F7. The optimized formulation was found to be F6

Keywords: Raloxifene hydrochloride, nanoemulsion, SNEDDS etc.,

Cite this article as:

Gayathri T, Venkata Ramana M, Rama Rao N, Formulation and Evaluation of Self Nano Emulsifying Drug Delivery System of Raloxifene Hydrochloride, Journal of Drug Delivery and Therapeutics. 2021; 11(4):16-19 DOI: http://dx.doi.org/10.22270/jddt.v11i4.4857

INTRODUCTION:

The quick identification of numerous highly potent novel chemical entities has resulted from the advent of combinatorial chemistry and high throughput screening. However, there has been a growing trend toward the identification of lead compounds with good therapeutic importance that fail to elicit their maximum therapeutic effects due to poor aqueous solubility. While these qualities work together to offer optimal drug-receptor binding properties, they also lead to poor drug solubility and membrane permeability. Many of these medications have poor and variable bioavailability since solubility and permeability are regarded criteria for oral absorption. The high dose-to-solubility ratio of such medications can be identified, and food coadministration typically increases bioavailability.[1]

Raloxifene hydrochloride (RLX) is a selective Estrogen-receptor modulator used to treat osteoporosis as well as breast and endometrial cancer prevention. The bioavailability of RLX is only 2% due to substantial pre-systemic clearance. The goal of this research was to customise and characterise RLX-loaded self-nanoemulsifying drug-delivery systems (SNEDDS) by using bioactive excipients that impact drug metabolism. [2]

MATERIALS AND METHODS:

Materials:

Raloxifene Hydrochloride was a generous gift from Delexcel Pharma Pvt. Ltd., Olive oil from Loba chemie Pvt. Ltd., Mumbai, India. Isopropyl myristate (IPM), Oleic acid Himedia Laboratories Pvt. Ltd., Tween 20, Tween 40, Tween 60, Tween 80 from Himedia Laboratories Pvt. Ltd., Mumbai, India. Propylene glycol Qualigen Fine Chemical, Mumbai. PEG 400 from SD Fine Chemicals Pvt. Ltd., Mumbai

Method:

Formulation of SNEDDS

Selection of SNEDDS Components Oil (solubility studies)

The shake flask method was used to determine the solubility of Raloxifene Hydrochloride in various buffers, oils, surfactants, and co-surfactants. The combination was maintained in sealed vials with an excess amount of medication added to 2 mL of each excipient. A vortex mixer (Remi, Mumbai, India) was used to facilitate the solubilization. Sealed vials were stirred in a water bath Figure 1: at 40°C for 24 h and allowed to reach equilibrium at 30°C for 72 h. Each vial was centrifuged at 15,000 rpm for 10 min using a centrifuge (Remi) followed by removal of the undissolved drug by filtering with a membrane filter (0.45 µm). Samples were suitably diluted with methanol and drug concentration was obtained via a validated UV method at 244 nm using methanol as a blank, using a double-beam UV visible spectrophotometer (Shimadzu 1700, Shimadzu, Tokyo, Japan). The experiment was repeated in triplicate and the results represent the mean value (mg/ mL± SD).[3]

Preparation of SNEDDS formulations

On the basis of the "Solubility studies" section, the oil (Olive oil), surfactants (Tween 20, Tween 40, Tween 60, Tween 80), and cosurfactants (PEG 400) were selected due to their

greater solubility enhancement effect on Raloxifene Hydrochloride. Various formulations were tried as shown in following Table. The formulations were prepared by dissolving Raloxifene Hydrochloride (8.04% w/w) in the mixture of oil, surfactant, and cosurfactant and were heated at 50 °C in an isothermal water bath. This mixture was mixed well and subjected to vortexing using cyclomixer (Remi, India), until a transparent preparation was obtained. All the mixtures were stored at ambient temperature for further use. [1]

Table 1: formulations of SNEDDS

Ingredients	F1	F2	F3	F4	F5	F6	F7
Raloxifene Hydrochloride	5%	5%	5%	5%	5%	5%	5%
Olive oil	20	20	30	30	40	50	50
Tween 80	54.5	69.6	61	52	35	46	44
PEG 400	25.5	10.4	9	18	25	4	6

Percent transmittance:

The sample was made by vortexing 0.1 mL of SNEDDS with 5 mL distilled water for 30 seconds. The % transmittance at 650nm was measured using a UV spectrophotometer.

Self-emulsification and precipitation assessment

In a brief, different compositions were classified based on the clarity and apparent stability of the resulting emulsion. Dropwise addition of the preconcentrate (SNEDDS) into 250 mL of distilled water in a glass beaker at room temperature was used for visual assessment. The ingredients were gently mixed with a glass rod or a magnetic stirrer at a speed of 100 rpm. They were observed immediately after dilution for assessment for self-nano emulsification efficiency, appearance (transparency), phase separation, and precipitation of drug. Precipitation was evaluated by visual inspection of the resultant nanoemulsion after 24 h. The formulation were then categorized as clear (transparent or transparent with bluish tinge), nonclear (turbid), stable (no precipitation at the end of 24 h), or unstable (showing precipitation within 24 h).

Characterization of SNEDDS

Droplet Size

Using a Zetasizer 1000HS (Malvern Instruments, UK), the droplet size of (SNEDDS) was estimated using photon correlation spectroscopy, which analyses variations in light scattering owing to Brownian motion of the particle. Light scattering was monitored at 25 ºC at a 90º angle. The optimized nanoemulsion sample was diluted by distilled water, placed in quartz corvette and subjected to droplet size analysis.[4]

Zeta potential Analysis:

Zetapotential of the optimum formulations was determined by dynamic light scattering using particle size analyser (Horiba scientific SZ-100, Horiba). The samples were diluted with a ratio of 1:100 (v/v) with distilled water and repeated in triplicate.[5]

Viscosity measurement:

The viscosity of SNEDDS was measured using small adapter of Brookfield cone and plate rheometer (Model LV2, Brookfield Engineering Laboratories, Stoughton, MA, USA) 12 rpm at room temperature (25 ±1°C), repeated in triplicate.[6]

Thermodynamic stability studies:

The optimum formula was subjected to further thermodynamic stability studies.

(1) Heating-Cooling cycle: Six cycles between 4°c and 45°c at each temperature for NLT 48hours were studied. The formulations that passed at this temperature without any signs of instability were subjected to centrifugation test.

(2) Centrifugation test: The formulations were centrifuged for 30 minutes at 3500 rpm. The formulations that did not show any signs of instability were chosen for the freeze-thaw cycle.

(3) Freeze-thaw cycle: The formulations were placed in temperature between -21° C and 25° C with storage at each temperature for NLT 48 hours. Passed formulations were centrifuged 5 minutes at 3000 rpm.[7]

The Morphology of SNEDDS:

Transmission Electron Microscopy Joel JEM-100 CX was used to examine the SNEDDS morphology. The SNEDDS samples were diluted in water (1:1000), and a sample drop was stained for 30 seconds with a 2 percent phosphor tungstic acid solution and deposited on a copper grid.[8]

RESULTS

SNEDDS preparation

The compatibility of oil, surfactants, and co-surfactants to acquire a higher transmittance was the essential foundation in the fabrication of nano emulsion. The preliminary ratio was tested to determine the quantity of oil (olive oil) surfactant (Tween 80) co-surfactant (PEG 400) for further characterisation. The effect of surfactant ratio on transmittance is presented in the below table. The effect of surfactant ratio on transmittance.

Table 2: Evaluation of SNEDDS Formulation

Oil(ml)	Surfactant(ml)	Co-surfactant(ml)	Transmittance (%)
1	1	1	9.32±5.21
1	2	1	54.00±2.10
1	3	1	71.20±13.39
1	4	1	97.53±0.95
1	5	1	97.83±0.96
1	6	1	99.21±0.69
1	7	1	98.65±0.35

Self-emulsification time:

Visual assessment was used to examine the self-nanoemulsifying characteristics of SNEDDS formulations, as stated. These tests were done on a variety of SNEDDS formulations. During the study, it was found that some formulations, F1, F2 and F3 showed turbidity, precipitation and thus was not stable, due to the relative increase in surfactant concentration and the presence of PEG 400. Hence, F4, F5, F6 and F7 were prepared with increased concentrations of surfactant. Formulation F6 could be mixed Olive oil, Tween 80, and PEG 400 and hence was selected as good formulation and subjected to further investigation regarding droplet size, Zeta potential, etc.[9]

Evaluation of SNEDDS for droplet size analysis, zeta potential, and drug content determination

Droplet size distribution following self-nano emulsification is a critical factor to evaluate a self-nanoemulsion system. The mean globule size of selected SNEDDS formulation F7, of Raloxifene hydrochloride was 148.5 nm is indicated the ability of the present technology to produce nanoemulsion that offers larger interfacial surface area required for drug absorption. An increase in the ratio of the oily phase resulted in a proportional increase in particle size, because of the simultaneous Increase in the s/cos ratio led to decrease in mean droplet size.

The F6 SNEDDS showed high absolute zeta potential value of -28.7 mv. The emulsion stability is directly related to the magnitude of the surface charge. Generally, an increase of electrostatic repulsive forces between nanoemulsion droplets prevents the coalescence of droplets. On the contrary, a decrease of electrostatic repulsive forces will cause phase separation. The results of zeta potential and drug content estimation are indicated in the given table. The percent drug content 99.21±0.69 of SNEDDS of Raloxifene Hydrochloride was found satisfactory.

Thermodynamic Stability:

The best formulation was found to pass the thermodynamic stress tests. The optimum formulation showed no signs of instability, indicating that the system was stable. The SNEDDS system should create a nanoemulsion through spontaneous emulsification in the digestive tract. The SNEDDS system must have sufficient quality to withstand stability in order to restrain creaming, cracking, or precipitating. The selected formulation was subjected to heating-cooling cycle, centrifugation, and freeze thaw exposure.[10]

Table 3: Evaluation of SNEDDS Formulation

Stability test	Replication 1	Replication 2	Replication 3
Heating-cooling cycle	Pass	Pass	Pass
Centrifugation	Pass	Pass	Pass
Freeze-thaw cycle	Pass	Pass	Pass

In vitro drug release study

An in vitro release study was conducted for pure drug and SNEDDs of Raloxifene Hydrochloride in different dissolution media such as 2 percent sodium lauryl sulphate, simulated gastric fluid (0.1 N HCl containing 0.5 percent of Tween 20), and simulated intestinal fluid to better understand the characteristics of drug release from SNEDDs (pH 6.8 buffer). The dissolution profiles of pure drug and SNEDDS formulation are shown in Figure 2. As evident from the drug release profiles, the pure drug evidenced meagre solubility of 27.52% in 60 min in 2% SLS, 20.6% in 0.1 N HCl containing 0.5% of Tween 20 and 20.93% in pH 6.8 buffer. The drug release from SNEDDS was markedly high such that 97.75% in 2% sodium lauryl sulphate, 95.73% in simulated gastric fluid (0.1N HCl containing 0.5% of Tween 20) and 96.25% in simulated intestinal fluid (pH 6.8 buffer). The results indicate instantaneous and remarkably high dissolution of Raloxifene Hydrochloride in all three media compared to the pure drug. This higher and faster dissolution rate Raloxifene Hydrochloride from SNEDDS is expected due to the nanoparticle size range of the particles offering higher interfacial area required for dissolution.[11,12]

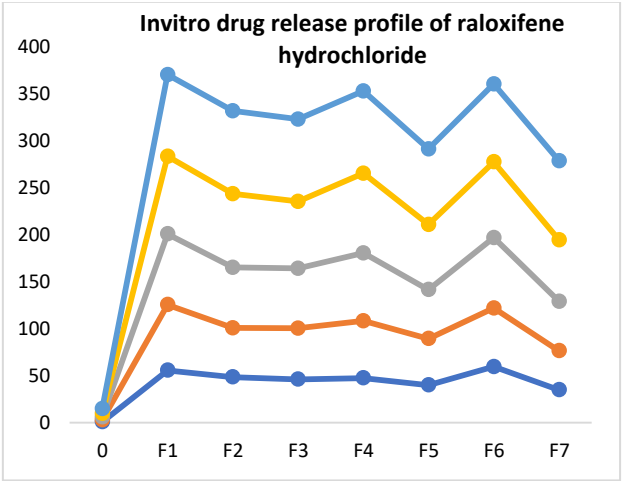

Figure 1: *In-vitro* drug release profile of raloxifene hydrochloride

Table 4: Evaluation parameters of self-nanoemulsifying drug delivery systems formulation of Raloxifene-HCl, F6

Evaluation Parameter	Results
Mean Droplet size (nm)	148.5±2.350
Mean Zeta Potential (mv)	-28.8±4.70
% Drug Found (mg mL^{-1})	99.69±6.1

CONCLUSION:

For oral administration, a SNEDDS containing Raloxifene hydrochloride was developed. Solubility studies, Pseudo ternary phase diagram creation, and droplet size analyses were used to determine the components and their ratio ranges for the formulation of SNEDDS. The ideal SNEDDS formulation featured adequate drug loading, quick self nano emulsification in aqueous media, and droplet sizes in the nano emulsion range.

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