



RESEARCH ARTICLE

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Development and Evaluation of Lapatinib Solid Lipid Nanoparticles in the Management of Breast Cancer

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ABSTRACT

The current research was aimed at formulation of Lapatinib loaded solid lipid nanoparticles (SLNs) followed by evaluation for effective treatment of breast cancer. The formulations prepared by homogenization and ultrasonication and evaluated for zeta potential, particle size, polydispersity index, entrapment efficiency and *in-vitro* dissolution studies. Entrapment efficiency studies indicated proportional relation between concentration of lipid and the amount of drug entrapped. The physicochemical parameter evaluation data indicated 94.27% entrapment efficiency, 130 nm particle size and -19.9 zeta potential for stable formulation. The *in vitro* drug dissolution studies indicated that Lapatinib loaded SLNs (F6) formulated with Dynasan 116 and Egg Lecithin was suitable for anti-cancer therapy with higher drug dissolution rate.

Keywords: Lapatinib, SLNs, Solubility, Breast cancer, Dynasan, Egg lecithin.

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INTRODUCTION

Despite of administration by the oral route remains most popular method of drug delivery, significant problems arise due to varying physical, chemical or biological characteristics of drug. Improper solubility, instability in gastrointestinal tract, poor membrane permeability or first pass effect is some of the major hurdles that lead to non-acceptance of drug entities with potentiality. [1] The drug delivery systems based on lipids are means of by-passing few physical and chemical hurdles related to drugs that exhibit poor absorption profile from GIT. These potential systems

include the more conventional forms of emulsions and micro emulsions, as well as more recent ones like liposomes, microspheres and solid lipid nanoparticles (SLN). [2] SLNs are a type of drug carriers colloidal in nature that had their development in last decade as substitute for present established carriers like emulsions, micro emulsions, liposomes etc. Distinctive properties like large surface area resulting from decreased particle size and high drug entrapment make SLN an appealing option to enhance pharmaceuticals activity. [3] Enhancement of drug absorption by SLN is due to different types of core lipids that mimic

formation of chylomicrons, which guides the carrier and drug entrapped within to follow transcellular pathway of absorption. [4] SLN enhances the bioavailability of lipophilic drugs by increasing the oral absorption of these drugs. [5]

Lapatinib acts as tyrosine kinase inhibitor that checks the growth of EGFR/ErbB1 and HER2/ErbB2 epidermal growth factors. [6] Lapatinib in combination with capecitabine was first approved by USFDA in 2007 for treatment of breast cancer in metastatic and advanced patients. [7-9]

MATERIALS AND METHODS

Materials

Lapatinib received as gift sample from Aurobindo Pharma Ltd., Hyderabad. The triglycerides Dynasan 112 and 116 were gifted by Sasol, Germany. Poloxamer-188 procured from Fizek Chemicals, UP., INDIA. Egg Lecithin (Lipoid E80) was obtained from Lipoid, Germany. The reagents and solvents were of analytical reagent (AR) grade.

Preparation of Lapatinib solid lipid nanoparticles

Lapatinib (drug 10 mg), solid lipid (50/100 mg) and egg lecithin (100 mg) were mixed with 10 mL of methanol and chloroform (1:1) followed by complete removal of organic solvents by employing a Rota evaporator. The contents heated to a temperature of 5°C higher than melting point of the lipid to melt model drug-embedded lipid layer. Poloxamer 188 dissolved in water was heated to similar temperature of oil phase. The hot aqueous phase mixed with the oil phase, followed by homogenization for 4min at a rate of 12,000 rpm. Sonication (12T-probe) was then performed for 20 minutes to obtained hot emulsion of oil-in-water. Lapatinib loaded solid lipid nanoparticles obtained by subsequently cooling the nanoemulsion to room temperatures.

Measurement of entrapment efficiency

Entrapment efficiency determined by the chromatographic estimation of free drug in aqueous phase separated from oil phase by ultra-filtration technique. The equipment fitted with centriscart tubes (Sartorius, USA) that contain a sample recovery chamber whose base is fitted with a filtration membrane (M. Wt. 20,000 Da). [10]

Estimation of total drug content

An equimolar mixture of carbinol and chloroform used to dissolve 100µL of the SLN formulation followed by dilutions mobile phase which were then estimated for Lapatinib present by HPLC.

In vitro drug dissolution studies

Dialysis bag method was employed for *in-vitro* drug dissolution studies. The membrane used for dialysis (pore size 2.4 nm; molecular weight 12,000-14,000 Da) was soaked in distilled water overnight prior to use and 0.1N Hydrochloric acid with 2% polysorbate 80 was used as dissolution medium. About 1 mL sample was withdrawn from receiver compartment at predefined intervals of 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12

and 24 hour time points simultaneously replacing it with equal quantity of release medium. These samples analyzed for drug concentration using UV-Visible Spectrophotometer at 260 nm after proper dilutions. [11]

Characterization

Fourier Transform infrared Spectroscopy FTIR

FTIR studies performed using Shimadzu spectrometer (Japan). Samples were prepared as KBr pellets

Differential Scanning Calorimetry (DSC)

The DSC chromatogram was recorded by placing accurately weighed 10 mg sample on aluminum plate and increasing the temperature of pan at rate 10°C/min

Surface Morphology

The formulation was vacuum dried to thin film after being transferred to a spherical aluminum plate followed by observation under scanning electron microscope (Quantum 200E Instrument). [12]

Determination of Zeta Potential, Particle Size and PDI of SLNs

Malvern Zeta seizer was used to measure zeta potential, size of the particle and polydispersity index (PDI) of Lapatinib loaded SLN's (Nano ZS90). About 100µL of prepared SLN's was mixed with 5mL water to obtain measurement of 50-200 Kilo Counts per Second (KCPS). [13]

Stability Studies

The stability Lapatinib SLNs checked at room temperature and 4°C for 60 days followed by determination of particle size, polydispersity index and zeta potential.

Table 1: Composition of Lapatinib SLNs

Ingredient	Formulation code					
	F 1	F 2	F 3	F 4	F 5	F 6
Organic Phase						
Lapatinib	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Dynasan-112	50 mg	100 mg	150 mg	-	-	-
Dynasan-116	-	-	-	50 mg	100 mg	150 mg
Egg lecithin	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Chloroform:						
Methanol (1:1)	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Aqueous Phase						
Poloxamer-188	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
water	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

RESULTS AND DISCUSSION

Optimization of Process Parameters

Homogenization time

A homogenization time of 5 minutes yielded optimal particle size and PDI. No considerable effect was observed when homogenization time was further increased.

Ultrasonication time

An Ultrasonication time of 20 min yielded optimal particle size and PDI.

Lipid concentration

Lipid concentration was optimized to 100 mg in increasing trend in particle size that slowed drug release was observed when lipid concentration was increased beyond 200 mg.

Surfactant concentration

The optimized concentration of egg lecithin was 100 mg and Poloxamer was 1.5% w/v.

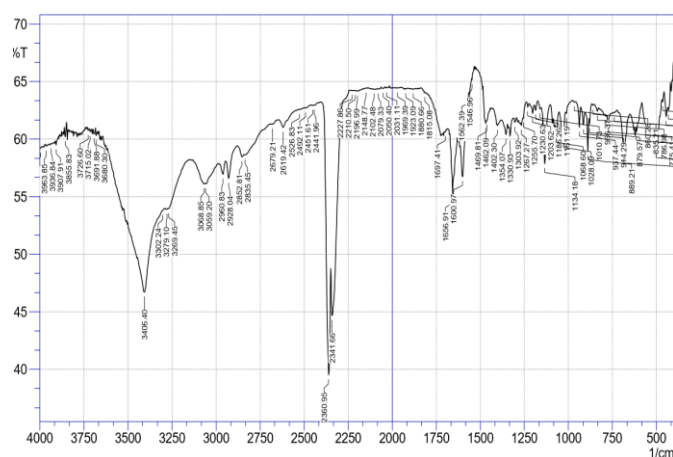


Fig. 1: FTIR Spectrum of Pure Drug of Lapatinib

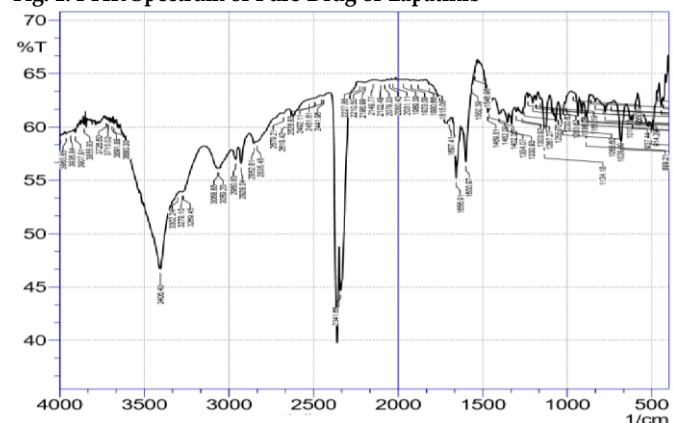


Fig. 2: FTIR Spectrum of SLN loaded Lapatinib

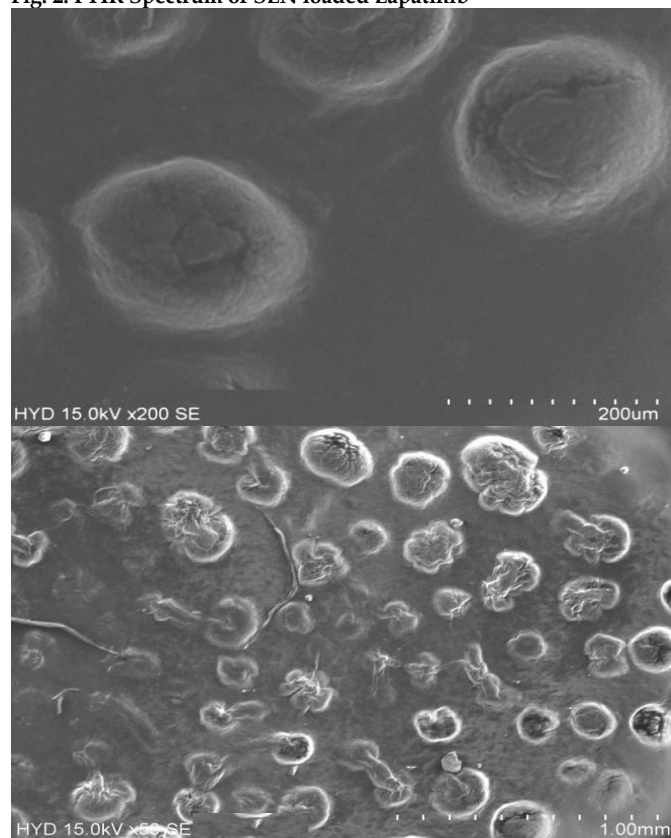


Fig. 3: SEM of Optimized formulation F6 Lapatinib SLN.

Effect of lipid concentration on entrapment efficiency (EE)

Entrapment efficiency (EE) was one of the important parameter and to attain optimum efficiency the factors

like type of lipid, its concentration and type of surfactant were considered. The EE of Solid lipid nanoparticles loaded Dynasan-112 and Dynasan-116 indicated an increase in EE with increase in lipid ratio. Results are tabulated and represented in Table 2. All formulations exhibited good entrapment efficiency that ranged from 88.39% to 94.27% with F6 formulation showing best entrapment efficiency.

Table 2: Entrapment efficiency and total drug content of SLNs (n=3)

Formulation code	Drug content (mg) $\pm$ SD	Entrapment efficiency (%) $\pm$ SD
F1	9.537 $\pm$ 0.022	88.39 $\pm$ 0.115
F2	9.149 $\pm$ 0.042	92.35 $\pm$ 0.248
F3	9.459 $\pm$ 0.016	90.27 $\pm$ 0.311
F4	9.349 $\pm$ 0.020	91.27 $\pm$ 0.049
F5	9.022 $\pm$ 0.006	92.34 $\pm$ 0.211
F6	9.891 $\pm$ 0.048	94.27 $\pm$ 0.222

Estimation of drug content

The maximum drug content of 09.891 mg was observed in formulation F6. The drug content of all prepared formulations is within 9.022-9.891 mg (Table 2).

The drug release from SLNs and suspension by dialysis method

The *in vitro* drug dissolution studies of Lapatinib SLN formulations were determined by Dialysis bag diffusion technique. Lapatinib-loaded SLN dispersions containing equivalent amount of drug was sealed in dialysis bag. The dialysis bag suspended in 250 mL of 0.1N Hydrochloric acid with 2% polysorbate 80 and stirred at 50 rpm at 37°C $\pm$ 0.5°C. The cumulative percent release was more initially during the first hour for pure drug and gradually the drug release was low when compared with other formulations and cumulative release of 97.49 $\pm$ 5.02% was noted for F6 formulation which was highest of all formulations and pure drug.

Characterization of prepared Lapatinib solid lipid nanoparticles

The presence of characteristic absorption bands of Lapatinib and the optimized SLNs containing Lapatinib suggest no interaction between the drug and excipients (Figure 1 and 2).

Drug-excipients compatibility study by DSC

DSC chromatograms of drug, excipients and drug-excipients mixtures (Figure 3) show thermograms of Lapatinib, Dynasan-112 and Dynasan-116 and the DSC thermograms of Lapatinib exhibits a sharp endothermic peak at 178.60°C

Scanning Electron Microscopy

The SEM micrograph indicates rod and spherical shape particles with smooth surface (Figure 4).

Zeta potential and Particle size of prepared SLNs

The particle size of SLNs determines the rate of drug release and drug absorption. Moreover smaller the particle size, larger is interfacial surface area hence improved bioavailability. The particle size of prepared SLN formulations ranged between 88.69 nm and 130.1 nm.

Table 3: *In vitro* dissolution studies of Lapatinib loaded SLNs (F1 to F6)

Time (h)	Formulation Code F1 to F6						
	Pure drug	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
1	55.22 ± 0.04	8.29 ± 0.26	10.27 ± 0.80	12.24 ± 0.85	13.36 ± 0.87	15.38 ± 0.95	16.89 ± 0.94
2	61.75 ± 0.45	12.37 ± 0.40	14.27 ± 0.86	18.27 ± 0.99	22.13 ± 1.04	24.18 ± 1.09	26.58 ± 1.09
4	69.75 ± 0.22	16.34 ± 0.16	21.28 ± 1.02	26.36 ± 1.20	30.45 ± 1.72	32.46 ± 1.98	35.18 ± 1.99
6	70.64 ± 1.45	25.17 ± 0.22	27.28 ± 1.20	34.45 ± 2.01	38.39 ± 2.04	40.32 ± 2.32	43.36 ± 2.36
8	71.22 ± 1.88	30.25 ± 1.75	32.36 ± 1.98	42.18 ± 2.32	45.78 ± 2.74	46.12 ± 2.35	49.39 ± 2.98
12	73.34 ± 2.01	39.27 ± 1.85	43.22 ± 2.32	51.39 ± 2.98	55.47 ± 2.45	58.32 ± 2.98	60.49 ± 3.26
16	75.53 ± 2.41	52.34 ± 1.42	53.28 ± 2.98	60.49 ± 3.18	63.26 ± 3.19	65.98 ± 3.20	69.39 ± 4.11
20	77.01 ± 2.78	60.47 ± 2.33	62.14 ± 3.18	70.39 ± 4.02	75.36 ± 4.80	79.45 ± 4.05	84.45 ± 4.83
24	80.19 ± 2.99	90.37 ± 2.42	93.45 ± 4.98	92.80 ± 5.01	94.27 ± 5.00	95.45 ± 5.01	97.49 ± 5.02

Table 4: Stability studies of the optimized formulation (F6) at both 25°C and 4°C for 60 days

Day	25°C			4°C		
	Size (nm)	PDI	Zeta potential (mV)	Size (nm)	PDI	Zeta potential (mV)
1	88.69 ± 1.45	0.517 ± 0.045	-22.9 ± 1.10	88.69 ± 1.58	0.517 ± 0.017	-22.9 ± 1.10
30	102.24 ± 5.27	0.521 ± 0.152	-21.24 ± 2.06	99.27 ± 2.84	0.519 ± 0.047	-21.1 ± 2.17
60	124.14 ± 8.29	0.533 ± 0.076	-20.24 ± 2.08	112.47 ± 3.47	0.521 ± 0.023	-20.6 ± 2.89

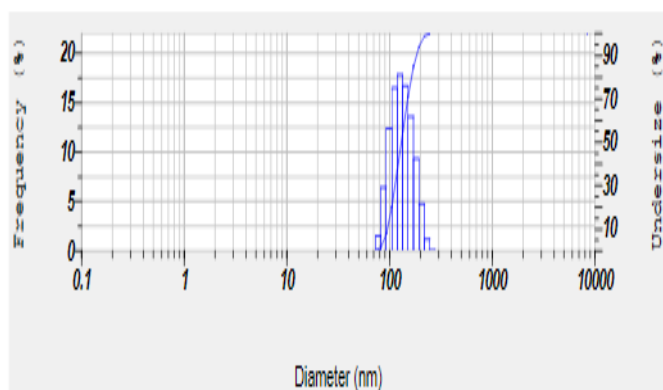


Fig. 4: Particle size analysis of optimized formulation (F6) of Lapatinib SLN

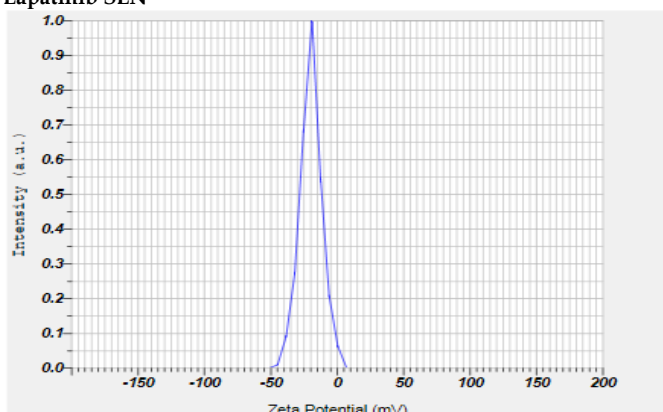


Fig. 5: Zeta potential of the Lapatinib SLN optimized formulation F6

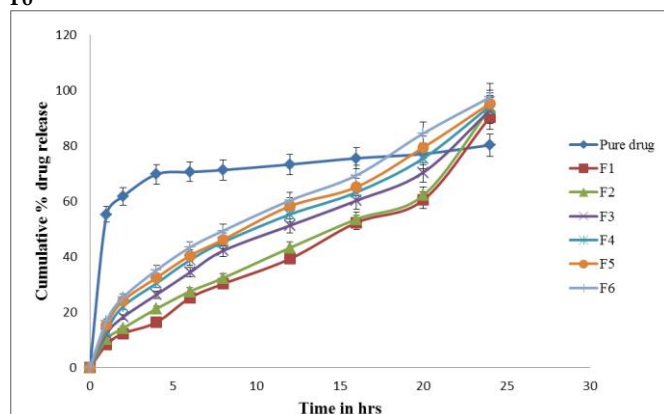


Fig. 6: Cumulative % drug release from Lapatinib SLNs

The Poly-dispersity index of SLNs was in between 0.398 to 0.731 and it was reduced to narrow range due to increasing concentration of surfactant.

The zeta potential of SLNs varies from -19.9 to -26.3 mV. The results indicate that formulations containing Dynasan-112 exhibited smaller particle sizes and larger PDI, zeta potential values. The formulations comprising Dynasan-116 (F6) exhibited better particle size and zeta potential values in comparison with other formulations.

Stability studies

Stability studies conducted for 60 days indicated no significant variations in the particle size, PDI, zeta potential, EE and drug release data of the optimized formulation (F6).

The SLNs were successfully formulated for Lapatinib by the process Homogenization and Ultrasonication. These are economically manufactured from Dynasan-112, Dynasan-116 and Egg Lecithin etc. The prepared formulations characterized for particle size, PDI, Zeta potential, DSC, scanning electron microscopy, entrapment efficiency and *in-vitro* drug dissolution studies. Results indicated that increase in the concentration of Lipid content lead to higher entrapment efficiency. A controlled drug release was observed in *In-vitro* drug dissolution pattern of SLN. Thus, results conclude that the Lapatinib loaded SLNs are effective drug carrier with increased solubility and bioavailability.

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