RESEARCH ARTICLE

Design and Development of Solid Lipid Nanoparticles Drug Delivery Systems for Prolonged and Targeted Delivery of Fulvestrant

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ABSTRACT

The research aims to design, formulate, and assess desired SLNs for poorly soluble anticancer drug Fulvestrant. The SLNs were made up of solid dispersion by high shear mixing and high pressure homogenization to make a very fine suspension. Drug loading, entrapment efficacy, particle size, and stability are the general parameters that were considered in this case for the different formulations; hence, optimization was performed through them. A good place to prove this preparation is an investigation of the saturation solubility of the Fulvestrant in various solvents, and subsequently determining which of them is clearly shown in 0.1 N HCl. Various observations of thermal analysis, that is DSC and XRD, indicated that the nanoparticles had stable, crystalline-like structure and, at the same time, favorable thermal properties. The optimized Batch B formulation was the one showing the highest drug loading and very high entrapment efficiency of about 70.8 and 95.2%, respectively. The particles normally had 150-nm size, while zeta potential was measured to be -220 mV. Ex-vivo diffusion studies successfully verified the drug release profiles of the nanoparticles, and the findings implied that Batch B exhibited 99.1% cumulative drug release for a 12-hour period. The pharmacokinetic studies indicated that the drug was released at a controlled rate and it had caused an increase in Tmax, which implied that there was an extended action of the drug. Stability studies verify Batch B as stable in both accelerated and long-term conditions. These studies flag the much value-adding potential of these SLNs as a good vehicle capable of delivering the improved pharmaceutical characteristics noted earlier for Fulvestrant.

Keywords: Solid Lipid Nanoparticles, Fulvestrant, Drug Delivery, Microemulsion Technique, Sustained Release, Cancer Treatment, Pharmacokinetics, Stability Studies

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INTRODUCTION

Breast cancer is second largest assassination disease in the world that caused a large proportion of cases by hormone receptor-positive (HR+)[1]. Fulvestrant, an estrogen receptor antagonist and selective estrogen receptor downregulator (SERD), is a key healing agent for managing HR-positive breast cancer, particularly post-menopausal women[2]. Effective results have been shown in treatment but its clinical application has been significantly restricted on account of issues such as poor solubility in an aqueous medium, low bioavailability, and necessity for frequent intramuscular administration resulting in patient noncompliance[3].

Nanotechnology, in present day, offers many encouraging prospects relative to overcoming such limitations of pharmacokinetics and pharmacodynamic profile of therapeutic agents[4]. Some of the various nanoparticles can go as Solid Lipid nanoparticles (SLNs) and nanostructured carriers (NLCs)[5]. These nanoparticulate systems have the potential to encapsulate a larger quantity of a medicine into nanoformulations, are stable, and are biocompatible, all of which make them valuable carriers. Advances in using this technology include the optimized solubilization of drugs, targeted drug delivery, and controlled release, giving favorable therapeutic effects without the presence of systemic effects[6].

SLNs have been used widely inmanaging of severalmethods of cancer due toexclusive feature of targeted tumor cells through passive targeting using enhanced permeability and retention effect[7]. However, in order to produce it with improved characteristics, surface functionalization with different ligands can be considered for targeting the tumor cells more clearly ensuring more clientele for chemotherapeutic agents through passive targeting mechanisms[8]. Nanoparticles prepared with Generally Recognized as Safe (GRAS) excipients have an amazing safety profile as they are meant for clinical uses[9].

The existing study emphases on design, development, and evaluation of nanoparticles designed for delivery of Fulvestrant. By addressing challenges of poor solubility and systemic toxicity, this research aims to boost therapeutic efficacy of Fulvestrant whereasabating its side effects. The study involves the optimization of formulation parameters, characterization of nanoparticles, and assessment of their drug release profiles. Furthermore, a comparative analysis with other nanocarrier systems, such

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Table 1: Composition of Optimized Fulvestrant-loaded Solid Lipid Nanoparticles (SLNs)

Ingredient		Batch A	Batch B	Batch C	Batch D	Batch E	Batch F
Fulvestrant (mg)	API	5	10	5	10	5	10
Glycerol Monostearate (GMS) (mg)	Oil phase	50	50	-	-	-	-
Witepsol W-35 (mg)	Oil phase	-	-	50	50	-	-
Stearic Acid (mg)	Oil phase	-	-	-	-	50	50
Egg Lecithin (%)	Lipophilic surfactant	1	1	1	1	1	1
Poloxamer (%)	Hydrophilic surfactant)	1.5	1.5	1.5	1.5	1.5	1.5
Sucrose (1%) (mg)	Improve redispersibility	1	1	1	1	1	1

as liposomes and nanoemulsions, is conducted to establish the superiority of nanoparticles in achieving prolonged and targeted drug delivery.

MATERIAL AND METHODS

Materials

Fulvestrant was kindly provided by R & D Center, Cipla Ltd, Vikroli, Mumbai. Stearic acid and Glyceryl monostearate was bought from S.D. Fine Chemicals Ltd., (Mumbai, India).Lipoid GmbH of Germany supplied the egg lecithin. The American company Sigma Aldrich supplied the Poloxamer and Witepsol W-35. All of the chemicals utilised in the research were of analytical or HPLC grade, and these particular materials are of a pharmaceutical grade.

Solubility Studies: An evaluation of solubility of Fulvestrant encompassed water, ethanol, and methanol as well as dimethyl sulfoxide (DMSO) and other organic solvents to assess the range of its physicochemical characters. Approximately 10 mg of Fulvestrant was accurately weighed and introduced into 10 ml solvent. Consequently, vials holding these samples were introduced into a reciprocal shaker at 25 °C and shaken for 24 h to reach equilibrium. After period of exposure, filtrate was sieved through a 0.45 µm membrane filter. Resultant solubility was further quantitated by HPLC in defined evaporation conditions. The solubility behavior was then analyzed to recommend further formulation development. A major solvent or mixture of solvents for possible further trial may appear in the analysis of data[10].

Melting Point: The microcrystalline powder sample is packed into an airtight capillary tube and then kept in the melting point equipment for heating. The initial and complete melting temperatures of the sample are recorded. Therepetitions were done three times for accuracy[11].

High-performance liquid chromatographic (HPLC)

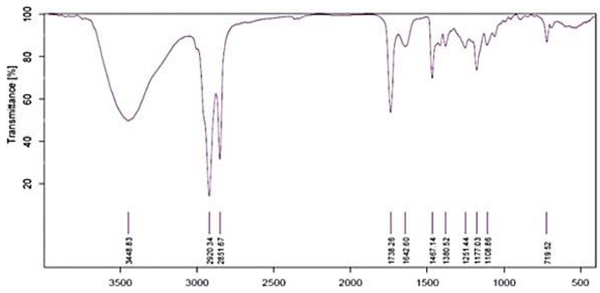

Figure 1a: FT-IR spectra of Reference standard

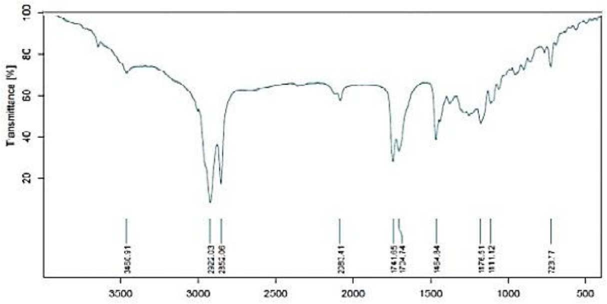

Figure 1b: FT-IR spectra of Sample of Fulvestrant

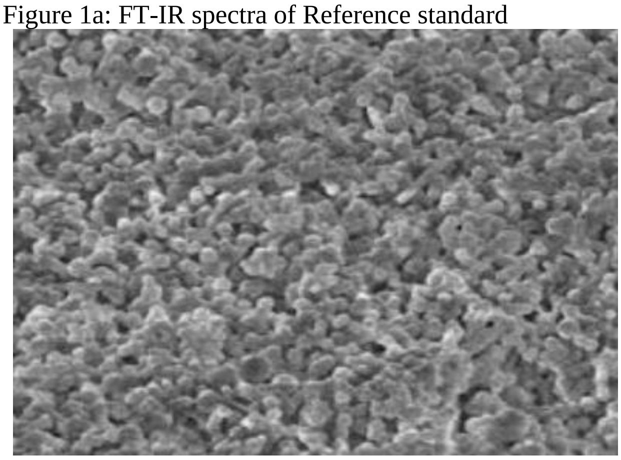

Figure 2: SLN Formulation Electron Microscope

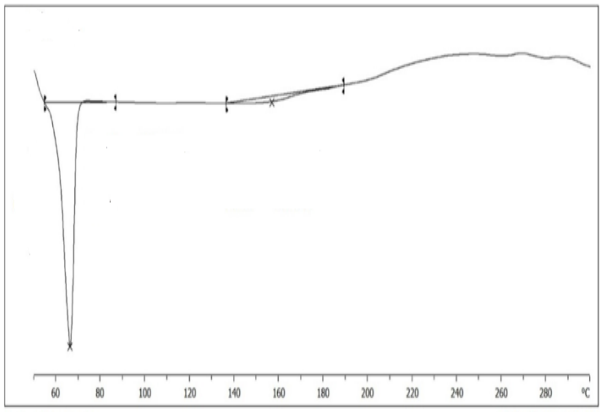

Figure 3: DSC of Fulvestrant Nanoparticles Complex

Table 2: Fulvestrant Solubility in various Media (mean±S.D., n = 3)

Solvent	Solubility (mg/mL)
0.1 N HCl	175.4 ± 4.3
Phosphate Buffer pH 6.8	0.120 ± 0.002
Phosphate Buffer pH 7.4	0.115 ± 0.004
Distilled Water	0.097 ± 0.032

technique for investigation of Fulvestrant was used described by Ghosh et al. (2021). The system comprised a Zorbax SB-C8 column of dimensions 4.6 mm x 150 mm, 3.5 µm. The column temperature was maintained at 40°C, with sample at 25°C. Mobile phase was mixed by using water/acetonitrile/methanol in the following proportions: The volume of mobile phase A is 410-mL water, 320-mL acetonitrile, and 270-mL MeOH, having composed mobile phase B with 100-mL water, 490-mL acetonitrile, and 410-mL MeOH. And flow was 1.7 mL/min-rate Burdened Eviction-of injection volume was 20 µL of sample.

Gradient elution program was carried out, with the mobile phase composition being modified during time under investigation. Precisely, during the first 0 min, the mobile phase was composed of 100% A, until 16 min passed and from the 16 min to 55 mins, composition was converted into 0% A and 100% B, and coinjection 55 min to 65 minutes 0% A and 100% B. By 66 min to 70 min fully returned to 100% A and 0% B. The detection was at a 282 nm wavelength and each analysis run in a typical 70 min.[12]

Characterization of Active Pharmaceutical Ingredients: The active pharmaceutical ingredient fulvestrant refers to a series of analytical methods to evaluate the purity, stability, and compatibility of its formulation with excipients. Design a scan within wavelength of 4000 to 400 cm^{-1} in the mid-infrared region. AT-FTIR was used for analysis[13,14].

Preparation of Nanoparticles

SLNs loaded with fulvestrant were prepared throughsolid dispersion by high shear mixing then high pressure homogenization. The Egg lecithin Glycerol Monostearate (GMS), Witepsol W-35 (a hydrogenated vegetable oil), and Stearic acid melted at 60°C.The Active pharmaceutical ingredient fulvestrant is dispersed to the lipid dispersion at 60°Cand after dispersion its been rapidly cooled to – 180 °C using liquid nitrogen. Thisfulvestrant lipids solid solution is dispersed under high shear mixing at 6000 to 8000 rpm in Poloxomersurfectant solution. The particle size of the crudedispersionwas reduced using high pressure homogenizer at 18,000 to 20, 000 psi for 6-8 passess to achieve the desired particlesize. 1% sucrose is added to the FLV - SLN suspension to improve dispersibility for lyophilisation by variable formulation factors as amount of lipids per batch, stirring time, high shear mixing speed, and surfactant concentration, optimization was carried out for the smallest particle size that would produce an ideal result (Table 1).FLV-SLN suspension is then lyophilized using a lyophilizer.

Evaluation of Nanoparticles

Measurement of Size and Zeta Potential

Table 3: Results of particle size and zeta potential

Batch	Particle Size (nm)	Zeta Potential (mV)
Batch A	220 ± 5	-18.5 ± 1
Batch B (Optimized)	150 ± 5	-26 ± 1
Batch C	180 ± 5	-20 ± 1
Batch D	210 ± 5	-22 ± 1
Batch E	250 ± 5	-15 ± 1
Batch F	240 ± 5	-16 ± 1

Table 4: Drug loading and entrapment efficiency

Batch Code	Drug Loading (%)	Entrapment Efficiency (%)
Batch A	45.3 ± 2.3	78.5 ± 2.9
Batch B (Optimized)	70.8 ± 2.4	95.2 ± 2.3
Batch C	47.6 ± 2.7	80.1 ± 3.4
Batch D	66.2 ± 2.9	93.5 ± 2.6
Batch E	43.7 ± 3.0	76.3 ± 3.1
Batch F	64.5 ± 3.2	92.1 ± 2.8

Table 5: Enthalpies, Melting Peaks, and Crystallinity of Bulk Lipids and Lyophilized SLN

Batch	Melting Peak (°C)	Enthalpy (ΔH, J/g)	Crystallinity (%)
Batch A	65.3 ± 1.2	1.58 ± 0.03	78.2 ± 3.1
Batch B (Optimal)	66.2 ± 1.0	1.73 ± 0.02	82.3 ± 2.5
Batch C	64.9 ± 1.3	1.45 ± 0.05	76.4 ± 3.2
Batch D	66.0 ± 1.1	1.68 ± 0.04	80.1 ± 2.7
Batch E	65.7 ± 1.0	1.52 ± 0.03	77.9 ± 3.0
Batch F	66.4 ± 0.9	1.75 ± 0.02	83.0 ± 2.3

Using a Malvern Zetasizer Nano ZS90 (Malvern Instruments, Worcestershire, UK), we measured the size and zeta potential of hereditary SLNs. At 25°C, disposable plain folded capillary zeta cells were utilised to measure the zeta potential, and disposable polystyrene cells were utilised for the particle size analysis. Prior to determining the zeta potential, the SLN dispersions were appropriately diluted using their initial dispersion medium[15].

Drug Loading Capacity and Entrapment Efficiency

The procedure outlined by Ye et al., 2008 was followed to determine the drug loading and drug entrapment effectiveness of lyophilised SLNs of Fulvestrant. For purpose of lipid precipitation, a solution containing 5 milligrammes of SLNs in 0.1N hydrochloric acid was heated in a water bath at 70 degrees Celsius for 30 minutes. After removing the mixture from the bath, it was left to cool to room temperature. After centrifugation at 4000 rpm for 15 minutes, the supernatant was collected and analysed using HPLC to determine the drug content.[16].

Scanning Electron Microscopy: The surface area and shape of the nanoparticles were studied under an electron microscope at the SEM. Mounted on a metal stub is a small amount of the sample. After being covered through gold by a sputter coater, sample is observed under SEM at various magnifications[17].

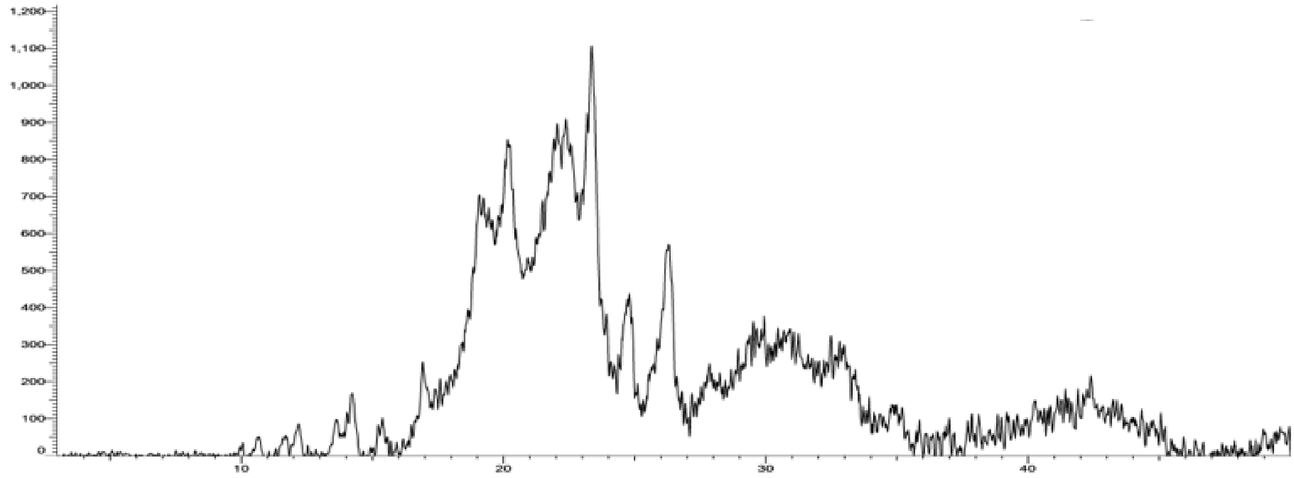

Figure 4: TGA curve of Fulvestrant Nanoparticles Complex

Differential Scanning Calorimetry: DSC investigation was conceded out through a DSC Q200 (TA Instruments, USA). The samples, in exactly 5 mg samples, were heated at 10oC/min over a range of 20-210oC. Equipment was positioned in a column above a nitrogen gas flow rate of 50 mL/min to conduct the analysis. An empty pan was utilised as a comparison, and standard aluminium sample pans are used[18].

X-Ray Diffraction (XRD): The crystallinity of drug and excipients existing in formulation is analysed by XRD. The optimized formulation is exposed to X-rays, and the diffraction patterns are recorded. Any alterations or shifts obtaining in results from with the typical diffractogram peaks show some alterations in crystallinity[19].

In-vivo Diffusivities: Release studies for Fulvestrant-loaded SLNs were carried out in vitro using the dialysis bag method. A solution of 0.1N HCl and phosphate buffer (PB pH 6.8) with 1% methanol was used for the investigation. Nanoparticles with a pore size of 2.4 nm were loaded into dialysis bags using dialysis membranes (Dialysis membrane-150, HiMedia, Mumbai, India) with a molecular weight cut-off of 12,000-14,000. Nanoparticles were kept in the dialysis bag whereas all free drugs were allowed to diffuse into the dissolving medium. Soaking the dialysis bags in double-distilled water for 24 hours is necessary prior to use. That was suspended in the dissolution media containing 0.41 mg equivalent drug per fraction and the drug release was measured at predetermined time[20].

Release Kinetics of Nanoformulation: To gain a better understanding of the release process, in-vitro data on drug release is fitted into various mathematical models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The model that fits best is determined by the value of the correlation coefficient (R^2)[21].

Stability studies

The formulation was tested for its Physicochemical stability as per ICH Q1(A) R2 guidelineunder an accelerated as well as under long-term storage condition. The samples were retainedat 40 ± 2°C and a relative humidity (RH) 75± 5%, and for a long-term period, it is kept at 25 ± 2°C and 60 ± 5% RH. At 1-month (1M) and 3-months (3M) and 6-months (6M) intervals, various parameters such as physical observation, pH, viscosity, osmolality, assay of Fulvestrant, total impurities, particle size, and zeta potentials. In vitro drug release study along with T25%, T50%, T75%, and T90% release were done. Data were collected and analyzed for the stability of the formulation under various conditions of storage[22,23].

Pharmacokinetic studies

Pharmacokinetic trials were conducted in Beagle dogs (three males and three females), with a single intramuscular dose of 20 mg/kg using reference and FLV SLN suspension formulations. A site of injection was marked over deltoid muscle, and dogs were fasted for 12 hours prior to dosing. Blood samples from various time points, such as 0, 0.25, 0.5, 1, 2, 4, 8, 24, 36, and 48, were collected for serum drug concentration estimation via HPLC. Key pharmacokinetic parameters-Cmax, AUC, Tmax,t1/2, CL, and Vd-were also calculated using noncompartmental analysis via PKsolver Excel add-on. The body weight and clinical signs were also monitored throughout for animal welfare[24,25].

RESULTS AND DISCUSSION

Results of Saturation Solubility of Fulvestrant

Table 6: In Vitro Release Profile of Fulvestrant-Loaded SLNs
(Mean ± S.D., n = 3)

Time (hours)	Batch A (%)	Batch B (%) (Optimized)	Batch C (%)	Batch D (%)	Batch E (%)	Batch F (%)
2	18.2 ± 1.3	25.1 ± 1.1	17.8 ± 1.5	21.6 ± 1.2	19.1 ± 1.4	23.8 ± 1.3
4	34.5 ± 1.8	48.5 ± 1.4	32.8 ± 1.6	39.5 ± 1.3	36.4 ± 1.7	45.1 ± 1.5
6	49.8 ± 2.1	66.2 ± 1.8	46.7 ± 2.0	55.4 ± 1.9	51.9 ± 1.8	63.3 ± 1.6
8	62.3 ± 2.3	81.5 ± 2.0	59.5 ± 2.2	69.3 ± 2.0	65.0 ± 2.3	79.0 ± 2.1
10	75.4 ± 2.5	94.3 ± 2.3	71.3 ± 2.4	81.0 ± 2.5	77.5 ± 2.4	91.6 ± 2.2
12	84.2 ± 2.8	99.1 ± 2.4	80.5 ± 2.7	90.8 ± 2.7	87.6 ± 2.6	96.2 ± 2.3

Table 7: Release Kinetics Data for Fulvestrant-Loaded SLNs
(Correlation Coefficient (R2R^2R2) Values for Different Models)

Batch	Zero Order (R2R^2R2)	First Order (R2R^2R2)	Higuchi (R2R^2R2) (Best Fit)	Korsmeyer-Peppas (R2R^2R2)
A	0.895	0.912	0.975	0.934
B	0.921	0.936	0.991	0.958
C	0.878	0.902	0.967	0.922
D	0.887	0.918	0.981	0.946
E	0.891	0.925	0.979	0.939
F	0.915	0.934	0.985	0.954

Table 8: Results of Pharmacokinetic studies

Parameter	Reference Formulation (n=6)	FLV-Nanoparticles(n=6)
C max (ng/mL)	4069 ± 714	3617 ± 896
T max (hrs)	0.08	0.17
T1/2	29.39	23.94
AUC last (ng/mL. d)	14904 ± 3356	13227 ± 2807
AUC 0-t (ng/ml*d)	ng/ml*d^2	ng/ml*d^2
AUC 0-inf_obs (ng/ml*d)	ng/ml*d^2	ng/ml*d^2
AUMC 0-inf_obs (ng/ml*d^2)	ng/ml*d^2	ng/ml*d^2

As shown in Table 2, Fulvestrant has been more soluble in 0.1 N HCl (175.4 ± 4.3 mg/mL) than in all the other solvents. Saturation solubility of Fulvestand produced less in distilled water 0.097 ± 0.032 µg/mL.Fulvestrant (0.097 ± 0.032) exhibited poor solubility in distilled water, demonstrating a low aqueous solubility. These results confirm the great need for proper vehicle development intending to enhance its solubility and bioavailability.

Indeed, the observed melting point of Fulvestrant was 104.86°C, which is very appropriate for its referent literature value of 104-106°C recorded. It points to the purity and homogeneity of the drug sample material used in the study. All characteristic peaks conforming to functional groups in molecular structure of Fulvestrant were found within the reference range, confirming the identity of Fulvestrant. However, the presence of absent peaks that typically characterize the functional groups of Fulvestrant, when visible, shows a potential reactivity of this active moiety with the excipients utilized in the formulation as Figure 1 depicts.

Results of Preparation and Optimization of SLN

SLNs have been prepared using many methods with different researchers. In present report, a simple, economic, and reproducible technique was employed for the preparation of SLNs based on solid lipid dispersion technology combined with high shear mixing and homogeniziation. Lipid Nanosuspesionare a lucid solution of light blue appearance that contains a lipophilic phase, surfactant, also co-surfactant and water as well.

For example, to make a drug lipid dispserion with a solid lipid, lipids must be made at a temperature over its melting point. They described different amounts of lipids in the study (50 mg, 100 mg, and 200 mg) for lipid optimization. What they noted was that with the application of high lipid concentrations, microparticles were designed as the quantity of lipid was precise high associated to amount of surfactant used.

This could be taken to mean that the concentration of the surfactant was lower than the optimal capacity to cover the lipid microemulsion drops and thereby the reduction of

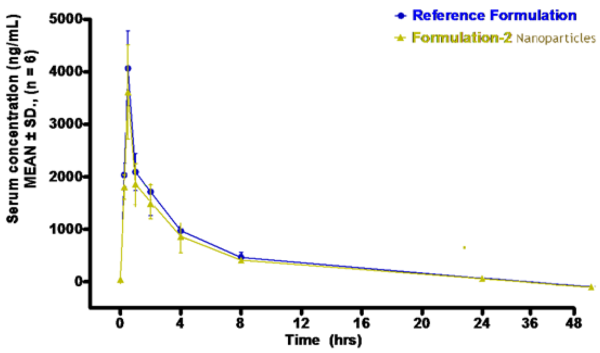

Figure 5: Serum concentration time profile of Pharmacokinetic studies

surface tension, causing the addition to cold water to produce microparticles and bigger droplets. Methods for creating SLNs that are both smaller and more stable were assessed. Particle size was studied by manipulating one variable at a time while keeping the other variables constant. These variables included formulation and process parameters such stirring time, stirring speed, and aqueous surfactant concentration.

Optimum conditions for these variable sets were determined based on the study results and then used for further assessment. The particle size could vary with the high shear mixing and homogenization at different speed, pressure, and the surfactant concentration of 1.5% w/v, which yielded the smallest size with narrow size distribution.

For drug-loaded batches, Fulvestrant was used as the active ingredient, and the lipids selected for this study were stearic acid, Witepsol W-35 and glyceryl monostearate. The lipophilic surfactant was poloxamer 188, and the aqueous surfactant was egg lecithin.

Particle size and zeta potential

Batch B is the most promising formulation analysing Table 3. Batch B stands out in this table as a formulation for drug delivery. It has the particle size of 150 nm and zeta potential of -26 mV; therefore, it is ideal for drug

Table 9: Fulvestrant Nanoparticles - Stability Data (Optimized Batch)

Parameter	Initial analysis	Accelerated (40 ± 2 °C/ NMT 25% RH)		Long term (25 ± 2 °C/40 ± 5% RH)	
		1 M	3M	1M	3M
Description (After Reconstitution)	Translucent	Translucent	Translucent	Translucent	Translucent
pH	7.0	7.5	7.2	7.1	7.3
Viscosity (cps)	7	6	6	6	7
Osmolality (mOsmol/kg)	320	323	328	342	340
Assay Fulvestrant (%)	98	101	105	102	104
Total Impurity	0.19	0.23	0.21	0.25	0.28
Particle Size (nm)	228	235	225	231	237
Zeta potential (mv)	-14.98	-15.45	-15.57	-15.89	-16.03
In vitro drug release					
T25% (h)	34.85 %	38.45 %	37.80 %	38.91 %	36.66 %
T50% (h)	37.35 %	43.86 %	42.66 %	44.50 %	43.50 %
T75% (h)	39.08 %	49.67 %	46.50 %	49.80 %	47.20 %
T90% (h)	42.98 %	52.09 %	54.10 %	56.42 %	53.81 %

release, especially in enhancing stability and reducing aggregation. This is something that other batches such as Batch E and F unfortunately will not have as they have higher particle sizes and smaller zeta potentials, implying they may have issues with stability and aggregation. Based on given features, Batch B is having possibilities for further development.The batch B of table 4 data denoted the highest values of drug loading and entrapment efficiency, with 70.8% and 95.2%, respectively. Batches D and F showed the higher drug loading; both of them sharing 66.2% and 64.5%, whereas 93.5% and 92.1% of the drug was entrap, respectively. The results clearly state that the increase in lipid is positively contributed by the increasing drug encapsulation. In contrast, point by batches A, C, and E is very low values like a rise in lipid ratio also augments entrapment efficiency and drug loading. Hence, this is the most ideal and useful sign for retreat preparation and eventual investment optimization; D and F also experienced round about promising options indeed special.

Results of Morphological Studies by Scanning Electron Microscope

We had some SCAN-Electron Microscopy as given in figure 2 to inquire after the Exact Exterior Morphology of the Nanoparticles. Most of them are said to appear within a nearly spherical shape. And all of the particles recorded by SEM were found to be the same according to Particle Sizing Measurements in the Particle Sizing Analyzer.

Results of Thermal Analysis by DSC

In this table 5, Batch B is selected as the ideal formulation, with melting peak, enthalpy, and crystallinity values that are higher and fall within the optimal range for lyophilized solid lipid nanoparticles (SLNs). The other batches have values that are close, but Batch B stands out as the most consistent and desirable formulation in terms of thermal properties and crystallinity.

In Table 5 B batch appears quite prominently batch finally evolved in Batch B with the melting peak, enthalpy, and crystallinity values floating somehow at a level higher and within the range of the optimal lyophilized solid lipid nanoparticles (SLNs). The other batches are a little bit close in silence, while batch B is easy in thermal properties and crystallinity; most of it is inevitable as a fair stand out test formulation. DSC gave a crystalline formation component DSC. Figure 3 gives DSC and 4 Gives XRD which also indicate the crystallinity of formulation.

Ex-Vivo Diffusion Studies

Table 6 provided detailed results of cumulative drug release. The percentage of drug release was the most considerable, reaching 99.1% in as much as 12 hours as may be seen from the results in table, obtained with batch B. This is because it has, together with its counterparts, some of the optimal lipophilic and hydrophilic surfactants balanced in conception of the lipid amount such that he has fashioned it in her strict intent for encapsulation that would allow for newer forms of sustained therapy. Differentiate here also-the performance of Batches of type F may ideally be ranked behind Batches of Type B because it is likely to give out 96.2% of its payload. These indicated lower bioavailability owing to a greater quantity of lipid in Batch F. Moderate drug release was found in Batches D and E, with Batches A and C demonstrating lower performance. Therefore, Batch B is most suitable in terms of maximum drug release as well as feasibility of an effective therapy.

Drug Release Kinetics

All bursts in the SLNs loaded with fulvestrant are properly resolved using different mathematical models that are integrated precisely for fitting the release data of the drug (Higuchi/korsmeyer Model. As the data demonstrate, Higuchi Model, on the one hand, might be the better representation of the release kinetics of the drug irrespective of the fact of R2>0.975R^2 > 0.975R2>0.975 for all batches as it involves a diffusion-controlled mechanism of drug release. Indeed, among formulations revealed in Table 7, Batch B showed highest R^2 value (R^2=0.991), thus proving it as very optimum formulation in terms of being optimized in both achievable and predictable drug release. Therefore, according to this study, Batch B would be potential for any kind of therapeutic applications because of its important formulation attributes in creating controlled-release profiles within the drug dosage form.

Pharmacokinetic studies

The pharmacokinetic study conducted with the reference formulation and FLV nanoparticles showed many differences in the key numbers which can be seen in Table 8 and depicted in Figure 5. The highest values of Cmax are those of the reference formulation, which reach 4069 ± 714 ng/ml while Cmax for the nanoparticles remains slightly below at a lower concentration of 3617 ± 896 ng/ml, demonstrating that absorption proceeds more rapidly for the reference formulation. A delayed Tmax of up to 0.17 hours is seen in the case of nanoparticles, while it is 0.08 in the case of the reference formulation, which suggests a slow onset of action. In fact, half-life (T1/2) of the nanoparticles is 23.94 hrs, as compared to the 29.39hrs of the reference formulation, suggesting faster elimination. Though less of AUC values is observed with the nanoparticles when compared with the reference formulation, they meedly exert a time-dependent environment.

FLV nanoparticles could provide a more controlled release profile with delayed Tmax and sustained drug exposure, hence making them possible as formulations for extended drug activity in therapeutic application. However, optimal results would bring its Cmax and AUC close to or surpass those of the reference formulation in terms of bioavailability.

Results of Stability studies

As indicated by the values in table 9, reconstitution results in a clear appearance all over different storage over 24 hours. The formulation remained very stable on the particular storage conditions. The pH was well within the biological acceptance range of 7 to 7.5 for all readings with minimal variations. The values of viscosity and particle size show minor changes, illustrating the good physical stability during storage. An increase in the Osmolality can be observed under accelerated storage conditions as a demonstration of slight changes in the concentration of solute. The test results show a 98% content level of fulvestrant, and the accelerated settings promote a higher level because of possible redistribution. Overall impurities are less but also show a marginal increase, particularly on long-term storage. Over time, the results of Zeta potential become negative to show slightly more electrical stability among colloid particles. There is a higher solubilization rate through testing dissolution parameters under accelerated conditions compared with native conditions, hence T90% (42.98% to 56.42%) exceeds that for native systems, implying improved performance of sustained solubilization on accelerated storage. Same with Batch B, this net formulation was stable across all conditions and showed better performance than the first, being with minimal impurity but maximum drug release. These characteristics further confirm the system's robustness for prolonged storage and therapeutic purposes.

CONCLUSION

High quality and targeted delivery of poorly soluble Fulvestrant has been facilitated by solid lipid nanoparticles purposely designed and formulated by Nanomedicine researchers for this purpose. The saturation solubility of Fulvestrant in 0.1 N HCl is considerably higher (175.4 ± 4.3 mg/ml) than phosphate buffer solutions (0.12 mg/ml) and distilled water (0.00387 mg/ml). Indeed, the high solubility profile of this drug indicates an urgent need for a suitable delivery system that can expand bioavailability of these drugs. Fulvestrant's melting point was 104–106°C, indicating that this high boiling point material is indeed of the purity that it must have for reliable development of drug formulations.

By using the solid lipid dispersion technique and subsequently subjecting it to high shear , producing SLNs proved with respect to underlying particle size, drug loading, zeta potential, and entrapment efficiency. formulated batch, the optimised Batch B, gave the best results in terms of its particle size, amounting to 150 nm, and zeta potential value of -26 mV which clearly indicated a stable and well dispersed nanoparticle system. This was the batch that produced the highest drug loading (70.8%) and good entrapment efficiency (95.2%). Thus, it was possible to rule out the best candidate for further development among the three batches. Although Batches D and F with higher lipid content demonstrated very good manners, Batch B proved to be the chief SLN over another batches of solid lipidnanoparticles formulation.

Batch B exhibit superior crystallinity and thermal characteristics with a melting peak at 66.2°C and a crystallinity of 82.3%, which was observed through various thermal analysis studies performed on the SLNs such as DSC and XRD. Possession of such a data indicates that there is no alteration in melting state of the particles, preventing any possible drug release. Batch B, in comparison to others, has performed highest with ex-vivo diffusion stages, which provide most drug release 99.1% during the first 12 hours. Moreover, these findings were in accordance with the data regarding Higuchi kinetics, and all the batches showed a good agreement with the Higuchi model. Batch B demonstrated the best correlation coefficient with 0.991 R2, meaning diffusion-based release.

Pharmacokinetic studies confirmed that FLV-loaded nanoparticles had controlled release profiles with delayed Tmax (0.17 hrs) compared to the reference formulation, which provided an onset of action period but prolonged exposure of the drug. The nanoparticles had shorter half-lives (23.94 hrs) compared to the reference formulation (29.39 hrs), indicating a faster elimination. Additionally, the AUC values reported by the nanoparticles are naturally higher than the reference formulation, pointing towards possible room for optimization towards better bioavailability.

The stability studies confirmed that optimized formulation (Batch B) maintained its physical and chemical stability under both accelerated and long-term storage conditions with features including pH partially stable, viscosity stable throughout and particle size, and drug release profile showed improved sustained release under accelerated conditions with notable change of T90% from 42.98% to 56.42%.

In short, designing and developing SLNs for FUL has confirmed to be a successful approach for increasing its solubility, stability, and sustained release. Among all, Batch B was considered to be unique and (function) close to the ideal, with a high potential for further development due to good drug loading, entrapment efficiency, stability, and drug release profile, among other attractive features. Given its potential, the findings underline SLNs as excellent candidates in the prolonged and targeted delivery of FUL, suggesting its promising therapeutic advantage in the treatment of cancer.

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