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Fabrication And Comparative Assessment Of Solid Dispersion And Nanosuspension In Solubility Enhancement Of Gefitinib

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Abstract

The purpose of this research was to develop a solid dispersion and a nanosuspension to improve gefitinib's solubility, and then evaluate and compare their efficacies. The SDS and NSP were prepared using solvent evaporation and precipitation methods respectively. Evaporating a hydro-alcoholic solution of GFT and HPMC at an optimum ratio (1: 5 w/w) yielded solid dispersions of GFT. A sufficient quantity of ethanol was used to dissolve the polymer. 3^2 complete factorial designs were used to optimize the NSP. Independent factors were Polo-188 (X1) and Tween-80 (X2), while dependent variables included polydispersity index (Y1) and particle size (Y2). The nine batches of NSP and SDS were created by adjusting the concentrations of the excipients. The drug concentration of NSP batches was found to be between 81.31 and 96.71%, with NSP 6 demonstrating the highest drug level of any batch tested, at 96.71%. SDS-7 had a PS of 251.7 nm, whereas NSP-6's PS was 131.8 nm. It was shown that although HPMC demonstrated a small solubility increase in the property of SDS-7 in all solvents, the most advanced NSP-6 formulation benefited from Polo-188's solubility augmentation. The results of this research indicate that gefitinib solubility was improved by the preparation of a nanosuspension.

Keywords: Nanosuspension; Gefitinib; Solid dispersion; solubility enhancement; HPMC.

Introduction

The development of new chemicals and generics is made difficult by their low water solubility. This unfavorable physicochemical feature is present in the vast majority of new drug candidates [1]. These compounds have limited oral bioavailability and absorption because they are poorly soluble. Some of the most common technologies used to enhance the biopharmaceutical properties of drugs include micronization, nanosizing, crystal engineering, the use of solid dispersions, molecular or lipid encapsulations, and other colloidal drug delivery systems like microemulsion formulation and self-emulsifying drug delivery systems [2, 3]. Based on factors including water solubility and in vivo bioavailability, the biopharmaceutics classification system places active

substances into distinct groups. When predicting the oral bioavailability of solid dose forms, BCS considers two key factors: solubility and intestinal permeability [4]. Low water solubility and high permeability categorize GFT as a BCS class II medicine. Tyrosine kinase inhibitors (TKIs) like GFT are a class of drugs. Kinases are proteins that regulate cell division and growth. Through the regulation of cytokine signaling and an uptick in lysosomal biogenesis, GFT prevents the spread of Mycobacterium tuberculosis [5]. As a receptor family, EGFR includes Her 1, Her 2, and Her 3 (erb-B1, erb-B2, and erb-B3, respectively). The bioavailability of GFT after oral administration is just 60% [6]. The liver is responsible for most of its elimination since it is mostly processed by CYP 3A4; its half-life is 48 hours. Solid dispersion, crystal engineering, salt generation, and complexation are only some of the strategies that have been explored to increase GFT's solubility in water. All methods are used to counteract the generalizability of this problem [7]. Nanotechnology is a new field of study in the pharmaceutical industry, and it is already being put to use to make poorly soluble medications more accessible. Nanoemulsion, nanoparticles, and NSPs are the most often used methods in nanotechnology [8]. NSPs are suspensions of nanoparticles of medication that have been stabilized by surfactants and are only marginally water soluble. NSPs improve the solubility and bioavailability of drugs. Precipitation, high-pressure homogenization, and solvent evaporation techniques including stabilizers and co-stabilizers are among the most used methods for NSP formation [9]. Because of its low solubility, GFT requires cutting-edge research and development [10]. Therefore, the purpose of this study was to synthesize GFT-NSPs in an attempt to improve the solubility of GFT. Nine different batches of NSP were first prepared through nanoprecipitation with Poloxamer-188 (Polo-188) and Tween-80 based on a design matrix. The produced batches were then analyzed for their drug concentration, entrapment efficiency, particle size, polydispersity index, and zeta potential. Based on these criteria, an optimization was selected and put through a battery of tests, including those for x-ray diffraction pattern, formulation shape, solubility, and in vitro drug release. The study's methodology and results are discussed in further depth below.

Materials and Methods

Acura Labs Pvt. Ltd. of Hyderabad, India, was where we made our acquisition of GFT. HPMC and poloxamer 188 were purchased from BASF India Ltd in Mumbai. Merck Ltd. in Mumbai, India received a request to acquire Tween 80. Merck Ltd. (Mumbai, India) supplied the DMSO used in this experiment. The investigation only used high-quality, analytical-grade compounds and excipients.

Methodology

The SDS and NSP were prepared by solvent evaporation and freeze drying as discussed in the subsequent section.

Preparations of GFT solid dispersion

Evaporation of solution of GFT and HPMC at an optimum ratio (1: 5 w/w) resulted in the preparation of GFT solid dispersions. A sufficient quantity of ethanol was used to dissolve the polymer. To generate a homogenous solid mass, the solvent was quickly evaporated with the help of moderate heat (up to around 50 °C) and surface airflow while being constantly vigorously stirred. The co-precipitate was crushed and vacuum desiccated for 24 hours, pulverized (again, following the development of a more fragile mass), vacuum desiccated for another day, sized into various sieve fractions, and kept in a desiccator until further characterization, as shown in Table 1[11].

Preparation of GFT nanosuspension

Using Design-Expert® (Version-7, Stat Ease Inc., MN, USA), 3^2 complete factorial designs were used to optimize the NSP. Independent factors were Polo-188 (X1) and Tween-80 (X2), while dependent variables included polydispersity index (Y1) and particle size (Y2). The nanosuspension precipitation method is used to prepare oral nanosuspension of GFT using different stabilizer and co-stabilizer concentrations. To sum up, 3 ml of DMSO was used as an organic solvent to dissolve 40 mg of GFT. Deionized water containing stabilizer Poloxamer-188 alone in different concentrations or in combination with co-stabilizer Tween 80, which acts as the antisolvent system. This was followed by the addition of the organic solution into the antisolvent solution at a very slow rate (1ml/min) with the help of a syringe pump, under mechanical agitation of different speeds using a homo disperser. To achieve the necessary nanosuspension, allow the organic solvent to evaporate for 60 minutes at 70±1 °C by transferring it to a hot plate magnetic stirrer. The batches were prepared according to the formulation design. [12].

Evaluations of SDS and NSP formulation

Percent drug content

10 mg of SDS and NSP formulations were thoroughly dissolved in 10 ml DMSO to determine the drug content by suitably diluting with water. The GFT concentration in the DMSO was measured using a spectrophotometer (UV 1700, Shimadzu, Japan) at 331 nm. Concentration vs percent drug content was calculated from the calibration graph [13].

Percent entrapment efficiency (%EE)

The percent EE is used to calculate how much medicine was included inside the manufactured suspension. The GFT concentration in the SDS and NSP was measured by ultra-centrifuging the samples at 5,000 rpm for 20 min (Bachman Coulter USA). After integrating the clear supernatant, a sample was diluted 1:10 (v/v) and the absorbance at 331 nm was measured using spectrophotometry (UV 1700, Shimadzu, Japan). The percentage EE was determined using the following equation (1)[14].

$$\%\mathrm{EE} = -\frac{\text{Amount of drug added} - \text{Amount of drug in supernatant}}{\text{Amount of drug added}} \times 100 - - - - - -(1)$$

Determination of particle size, and polydispersity index

PS is an important characteristic of effective SDS and NSP formulation because it can increase medication solubility and absorption through the oral route. Using a (Malvern Instrument Ltd. USA) Nano brook 90Plus and a +_20mW neon laser, the average PS and Polydispersity index (PDI) were determined. The experiment was carried out at a room temperature of 25 °C, at a 90° angle, using an expandable polymeric cell with a diameter of 10 mm and a run duration of 180 s. The samples were analyzed at room temperature after being diluted with distilled water at a ratio of 1:10 (v/v) [3,15].

Selection and Characterization of the Optimized Formulation

The improved formulation was named after the chosen desirability value was acquired after Design-Expert® Version-7 validated the accepted design. Based on the improved batch, the selection criteria were altered to have the lowest PS and PDI. The resulting batch was lyophilized using a (Virtis Ltd, USA, Benchtop freeze drier) and analyzed further.

X-ray diffraction (XRD) study

X-ray diffraction (XRD) analysis was performed on coarse powder SDS and lyophilized NSP to determine alterations in the internal structure of solvent-evaporated SDS and lyophilized GFT-loaded NSP. With a scan rate of 1°/min and a scan range of 2 in 3-90° (Bruker,08 Advance, Germany), XRD analysis was performed [16].

Morphological study

SDS and NSP were analyzed for their morphology using a scanning electron microscope (SEM). Both samples were coated in platinum, allowed to dry overnight at ambient temperature, and then scanned with a 20-kV electron beam [17]. The copper stubs were attached to the samples using double-sided tape.

Solubility study

Both the pure GFT and the two formulations were tested for their solubility in a water/DMSO/phosphate buffer (pH 1.2). Both formulations were tested for solubility by dissolving large amounts of GFT powder in 10 mL liquids in Teflon-facing, screw-capped vials. The vials were kept in an orbital shaking incubator (CIS-24, Remi instrument, Mumbai, India) at 37+/-0.5 °C and 100 rpm for 24 hours. Using a 0.22 m membrane filter (Merck Millipore®, Germany), we filtered the contents of the vials before measuring their absorbance at 331 nm using a UV spectrophotometer (1700, Shimadzu, Japan) [3,18].

In vitro dissolution study

In vitro dissolving studies were conducted on pure GFT, SDS, and NSP using an HI media dialysis membrane (MWCO 12 KD) dialysis bag. Pre-treated dialysis bags were filled with a volume of optimized NSP formulations containing 40 mg of GFT. At 37 +/-0.5 °C and 100 rpm paddle speed, the medication was dissolved in 900 ml of dissolution fluid using a USP dissolving device II. Drug release from the new GFT NSP and SDS formulations were compared to that of pure drug in a 0.1N HCl (pH 1.2) environment. 5 (ml) samples were taken and dissolved in fresh media at regular intervals (between 5 and 60 minutes). Filtering and UV analysis at 331 nm were used on the samples [19].

In vivo pharmacokinetic study

Since dissolving experiments showed that GFT nanosuspension had the maximum solubility and drug release, in vivo pharmacokinetic studies on GFT NSP were conducted in comparison to pure GFT.

Healthy Swiss albino rats of either sex between 2 and 3 months of age, weighing between 150-250 g were used for the study. The animals were housed in standard environmental conditions (12 h light and 12 h dark cycle, 25 ± 5 ^{0}C, 35-60% humidity); the animals were fed with a commercial pellet diet and tap water ad libitum. Before experimenting, the protocol was approved by the institutional animal ethical committee. As per the guidance of the committee for control and supervision of experiments on animals (CPCSEA). The pharmacokinetic study was performed in overnight fasted (16h) normal animals

Pharmacokinetic (PK) studies were conducted in overnight fasted animals to investigate the oral pharmacokinetics of GFT-NS at a dose of 50 mg/kg. Blood samples (0.25 ml) were collected from the tail vein at specific time points (30 min, 1 h, 2 h, 4 h, 6 h, 12h, and 24 h, n = 6). The blood was collected in heparinized microvet tubes, centrifuged at 12,000 rpm for 10 min to separate plasma, and stored at −80°C until analysis. Gefitinib was extracted from plasma using the protein

precipitation by methanol method and analyzed using high-performance liquid chromatography (HPLC) with a C18 reversed-phase column (Agilent 2000 series, Agilent Technologies, Germany), Ezchrome Elite Software, quaternary pump (Model G1354 A), and ultraviolet variable wavelength diode array detector (Model G1315D). As per the reported method, the mobile phase consisted of ammonium acetate (20 mM, pH 4.5) and acetonitrile, with a composition of 45% ammonium acetate and 55% acetonitrile at the time of injection. Pharmacokinetic parameters such as the area under the curve (AUC), maximum concentration (C_{max}), and time to reach maximum concentration (T_{max}) were analyzed using WinNonlin® 5.0 software, USA. [20].

Formulation of immediate release tablet of selected batch

Immediate-release tablets of optimized NSP formulation were prepared by direct compression method by adding suitable excipients as shown in Table 2. Four batches of tablets were prepared by mixing NSP formulation and excipients using glass mortar [21].

In vitro dissolution test for tablets

A USP dissolution test apparatus type 2 with a stirrer rotating at 50 rpm was used to perform dissolve rate studies on manufactured tablets in 900 mL of pH 1.2 USP dissolution medium comprising citric acid and sodium phosphate at 37°C ± 0.5 °C. At 5, 10, 15, 30, 45, and 60 minutes, 5 mL aliquots were extracted, filtered (0.45-m Millipore filter), diluted, and quantified at 331 nm using an ultraviolet (UV) spectrometer. Each sample's dissolution rate was calculated, and average values of cumulative drug release were obtained before the release curves were plotted [22].

Stability study

Accelerated stability testing was performed for up to 6 months at 25° C/60% RH on the optimized nanosuspension immediate release tablet (GFNST2), following ICH recommendations. There was a dissolution study and drug content analysis done every 60, 120, and 180 days [23].

Result and Discussion

Percent drug content

The concentrations of the excipients in the nine batches of SDS and NSP were varied. The drug concentration of NSP batches ranged from 81.31 to 96.71%; NSP 6 had the highest drug level of all batches, at 96.71%. Similarly, SDS revealed drug concentrations ranging from 80.12 to 93.23% across all batches. SDS 6 contained 93.23% drug as a result of the created formulations, NSP6 and SDS7 batches were chosen as optimal batches and submitted for further comparative analyses.

Percent entrapment efficiency (%EE)

The concentrations of the excipients in the nine batches of NSP and SDS were varied. The drug entrapment of NSP batches ranged from 71.3 to 96.61%, with NSP 6 showing the highest drug entrapment at 96.61%. Similarly, SDS demonstrated drug entrapment ranges of 70.2 to 93.3%. SDS 6 had 93.23% drug entrapment across all batches. As a result, batches of produced formulations NSP6 and SDS6 were chosen as optimal and submitted for further comparative analyses.

Determination of particle size and polydispersity index

The formulation's PS is critical to the solubility of medicinal compounds. The PS of SDS-7 and NSP-6 were 251.7 and 131.1 nm, respectively. The concentrations of the polymers HPMC and Polo-188

impacted the variation in PS in both formulations. The NSP had a lower PS than the SDS. As a result, it was a more vulnerable formulation to increased GFT solubility. The PS average diameter and distribution variance were used to calculate the PDI. SDS-7 and NSP-6 PDI values were determined to be 0.627 and 0.351 Mw, respectively. NSP-6 PDI between 0.6-0.2 value implies high levels of homogeneity within the sample, Figure 1.

Selection and Characterization of the Optimized Formulation

X-ray diffraction (XRD) study

Figure 2 shows the diffraction pattern indicating the change in the crystalline nature of the drug. The X-ray diffractogram of pure GFT showed its highly crystalline, marked by numerous distinctive peaks. Relatively fewer peaks were observed in the lyophilized nanosuspension of the drug. GFT nanosuspension XRD showed a lesser number of peaks than pure GFT. Nanosuspension caused a large change in the crystalline structure of GFT. It can also be predicted that a larger portion of GFT has been converted to amorphous form. The broader and less intense peak as compared to pure GFT at different angles shows the formation of an amorphous state

Morphological study

The SEM photomicrographs optimized freeze-dried GFT nanosuspension (NS6) and GFT solid dispersion are shown in Figure 3. Photomicrographs proved a great morphological difference between GFT nanosuspension (NS6) and GFT solid dispersion. GFT solid dispersion appeared as irregularly shaped crystalline forms while GFT nanosuspension appeared as plate and small spherical structures. SEM analysis confirmed a change in GFT spherical structure and shape during the precipitation process. The analysis also confirms the reduction in particle size which could alter the solubility and dissolution behavior of GFT. In both methods, nanosuspension showed good morphological structure comprised of solid dispersion method.

Solubility study

Solubility research was carried out to investigate the characteristics of both formulations in water, DMSO, 0.1N HCL, and pH 7.4 phosphate buffer. HPMC demonstrated a somewhat solubility improvement property of SDS-7 in all solvents, while Polo-188 increased the greatest solubility of advanced NSP-6 formulation. Based on the results, it was determined that NSP formulation increased GFT solubility more than SDS.

In vitro dissolution study

In a comparison investigation of GFT pure drug, SDS and NSP they demonstrated 26.25% drug release, whereas GFT dispersion and nanosuspension demonstrated 96.66 and 99.14% drug dissolution, respectively. When compared to pure drug, both formulations showed maximum dissolution, and when compared to SDS, NSP demonstrated maximum drug release, indicating that it improves GFT solubility by adding polo-188 and Tween-80. NSP demonstrated the greatest solubility in both formulations, thus in vivo pharmacokinetic research was undertaken on it. Figure 4 depicts a summary of the medication release research.

In vivo pharmacokinetic study

Both plain GFT and GFT nanosuspension (NS6) were orally fed to rats in in-vivo tests to establish their pharmacokinetic properties. C_{max}, T_{max}, AUC0-12, and F (relative bioavailability). After oral

administration, the median T_{max} for peak plasma concentration (C_{max}) of 2459.56 ± 66.27 ng/mL and 3467.12 ± 78.16 ng/mL for plain GFT and NSP 6 GFT nanosuspension, respectively. The mean AUC0-12 value for plasma concentrations across time was 5093.59 ng. h/mL and 7958.58 ng. h/mL, respectively. The results showed that GFT's nanosuspension had a relative bioavailability (F) of 140.96 %. The pharmacokinetic results showed that there were statistically significant changes in C_{max}, AUC0-12, and F between ordinary GFT and GFT nanosuspension, but no significant difference in T_{max}. This data provides strong evidence that GFT nanosuspension systems enhanced oral bioavailability. GFT's bioavailability (how well it works in the body) increases because the medication is more easily dissolved and absorbed (Figure 5).

In vitro dissolution test for tablets

The instant-release tablet dissolving profiles are shown in Figure 6 for both plain GFT (GFTT1 and GFTT2) and freeze-dried optimized nanosuspension (GFNST1 and GFNST2). Table 3 provides the dissolving rates for the identical formulations. Freeze-dried nanoparticulate instant-release tablets of GFT were compared to plain GFT immediate-release tablets in terms of their dissolving profiles. The results of the study demonstrate unequivocally that the dissolving rate of GFT tablets is much higher. GFNST2 tablets showed the fastest medication absorption and distribution. Reduced particle size to the nanometre range, increased surface area, and a change in particle shape may all contribute to the enhanced dissolving rate of freeze-dried nanosuspension tablets. The dissolving rate was further improved by the addition of Polo-188 to the NSP formulation, which increased surface wetness.

Stability study

Every two months, the samples preserved for stability study were taken out and analyzed for drug content and in vitro drug release. The drug content and in vitro drug release of the optimized immediate-release tablet (GFNST2) exhibited extremely small, non-significant variations. The optimized immediate-release tablets of freeze-dried nanosuspension (GFNST2) were stable over six months, as indicated in Table 4 of the stability research findings.

Discussion

The present study aimed to develop and compare solid dispersion and nanosuspension for gefitinib solubility enhancement. Nine batches were prepared of NSP and SDS as part of our experiment by altering the excipient concentrations. The drug concentrations in the different NSP batches varied from 81.31 to 96.71 %, with NSP 6 having the highest drug content of all batches at 96.71%. Similarly, SDS indicated that the drug concentration in all batches ranged from 80.12 to 93.23%. The drug content was 93.23% according to SDS 7. NSP6 and SDS7 batches were selected as ideal batches from the developed formulations and subjected to further comparative evaluations. To make the nine batches of NSP and SDS, the excipient concentrations were changed. NSP 6 had the greatest drug entrapment rate of all batches, at 96.61%, with the other batches' drug entrapment rates ranging from 71.3 to 96.61%. Similarly, SDS demonstrated drug entrapment ranges of 70.2 to 93.3%. Across all batches, SDS 7 revealed 93.23% drug entrapment. As a result, the batches of the optimized created formulations NSP6 and SDS7 were selected and submitted to further comparative examinations. The PS of the formulation has a considerable impact on the solubility of pharmaceutical compounds. SDS-7 and NSP-6 have PS values of 251.7 and 131.1 nm, respectively. The concentrations of the polymers HPMC and Polo-188 influenced the PS variation in both formulations. The NSP had a lower PS than the SDS. As a consequence, the formulation was

more susceptible to higher GFT solubility. The PDI was determined using the distribution variance and the PS average diameter. The PDI values for SDS-7 and NSP-6 were 0.627 Mw and 0.351 Mw, respectively. While the PDI score for SDS-7 and the PDI value for NSP-6 implies that the samples are homogeneous. The GFT dispersion diffractogram displays all important unique crystalline peaks. This demonstrates that the drug transformed just a little into its amorphous form. NSP-6 shows the conversion of a crystalline form of the drug to an amorphous form by reducing peak intensities. SEM photomicrographs of SDS-7 and freeze-dried NSP-6 revealed significant morphological differences between the two formulations. SDS appeared as little crystalline with irregular shapes, while NSP appeared as plates and small spherical structures. SEM research indicated that the spherical structure and shape of GFT changed throughout the precipitation process. The study also supports the reduction in particle size, which may alter the solubility and dissolving properties of GFT. In comparison to pure GFT, both SDS-7 & NSP-6 showed excellent morphology. Solubility research was carried out to assess the efficacy of both formulations to enhance solubility in water, DMSO, 0.1N HCL, and phosphate buffer at pH 7.4. It was discovered that HPMC somewhat improved the solubility of SDS-7 in all solvents, but Polo-188 improved the maximum solubility of advanced NSP-6 formulation. Based on the findings, it was established that the NSP formulation improved GFT solubility more than the SDS formulation. In a comparison investigation of GFT pure drug, SDS and NSP demonstrated 26.25% drug release, whereas GFT dispersion and nanosuspension demonstrated 96.66 and 99.14% drug dissolution, respectively. When compared to pure drug, both formulations showed maximum dissolution, and when compared to SDS, NSP demonstrated maximum drug release, indicating that it improves GFT solubility by adding polo-188 and Tween-80. NSP revealed maximum solubility in both formulations; hence, NSP underwent further in vivo pharmacokinetic study. In vivo studies were conducted to investigate the pharmacokinetic features of regular GFT and GFT nanosuspension (NSP6) administered orally to rats. The average peak plasma concentrations (C_{max}) of plain GFT and NSP 6 GFT nanosuspension after oral administration were 2459.56 and 3467.12 ng/mL, respectively, and the mean peak plasma time (T_{max}) was 2.4 hours. The AUC0-12 (area under the plasma concentrations-time curve) mean values were 5093.59 and 7958.58 ng/mL, respectively. The relative bioavailability (F) of GFT from nanosuspension was found to be 140.96 %. A statistical examination of the pharmacokinetic data revealed substantial differences in C_{max}, AUC0-12, and F between regular GFT and GFT nanosuspension, but not in Tmax. These data suggest that GFT nanosuspension systems improved GFT oral bioavailability. This enhanced activity is due to the drug's improved solubility and dissolution, which speeds up absorption and so increases GFT bioavailability. Dissolution characteristics of immediate-release tablets containing ordinary GFT (GFTT1 and GFTT2) as well as freeze-dried tailored nanosuspension (GFNST1 and GFNST2). The dissolving profiles of normal GFT instant-release tablets and freeze-dried nanoparticulate GFT immediate-release tablets were examined. The comparison clearly shows that GFT tablets greatly enhance the dissolving rate. Most drug was released from GFNST2 tablets. Increased surface area, reduced particle size to the nanometre range, and changed particle shape may all contribute to the higher dissolving rate of freeze-dried nanosuspension tablets. The Polo-188-induced increase in surface moisture in the NSP formulation increased the dissolving rate even further.

Conflict of Interest: Authors do not have a conflict of interest

Table 1: Design matrix of GFT-SDS formulation

Batches Code	Components

	GFT (mg)	HPMC (mg)	Ethanol (ml)
SDS 1	10	50	50
SDS 2	15	75	50
SDS 3	20	100	50
SDS 4	25	125	50
SDS 5	30	150	50
SDS 6	35	175	50
SDS 7	40	200	50
SDS 8	45	225	50
SDS 9	50	250	50

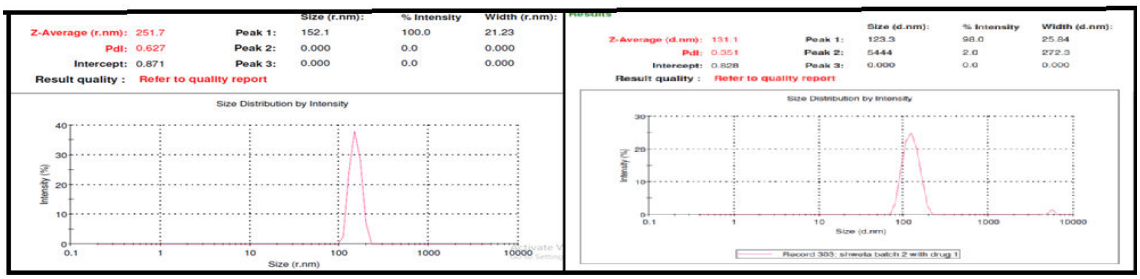
Batches Code	Components					
	GFT (mg)	Polo-188 X1 (mg)	Tween 80 X2 (ml)	DMSO (ml)	Purified water (ml)	String speed (rpm)
NS1	40	20	2.0	3	q.s. to100	3500
NS 2	40	30	3.0	3	q.s. to100	3500
NS 3	40	40	4.0	3	q.s. to100	3500
NS 4	40	20	4.0	3	q.s. to100	3500
NS 5	40	40	3.0	3	q.s. to100	3500
NS 6	40	30	2.0	3	q.s. to100	3500
NS 7	40	40	3.0	3	q.s. to100	3500
NS 8	40	20	2.0	3	q.s. to100	3500
NS 9	40	30	4.0	3	q.s. to100	3500

Table 3: Formulation of Plain GFT and NS6 immediate release tablet.

Sr. no	Ingredients	Formulations			
		GFTT1	GFTT2	GFNST1	GFNST2
1	NS6 (20 mg/50 mg) equivalent to Gefitinib	20	50	42	105
2	Microcrystalline cellulose (mg)	118	88	96	33
3	Sodium starch glycolate (mg)	6	6	6	6
4	Magnesium stearate (mg)	3	3	3	3
5	Talc (mg)	3	3	3	3
6	Total weight (mg)	150	150	150	150

Table 4: Drug content and in vitro release study immediate release tablets of freeze-dried optimized nanosuspension (GFNST2) after stability.

Formulations	Percentage Drug Released (n = 3, Mean ± S.D)					
	Time (min)					
	5	10	15	30	45	60
GFTT1	4.55 ±0.34	7.32 ±0.52	10.21 ±1.33	17.1 ±1.61	24.28 ±2.57	29.42 ±3.14
GFTT2	6.24 ±0.40	12.18 ±0.88	13.87 ±1.07	22.59 ±1.38	27.92 ±3.36	33.23 ±3.53
GFNST1	10.42 ±0.12	32.66 ±0.29	65.54 ±1.46	79.53 ±2.16	88.25 ±2.89	93.98 ±3.02
GFNST2	11.45 ±0.07	36.22 ±0.51	67.74 ±1.36	81.40 ±2.12	89.22 ±2.87	97.79 ±3.09



A) PS and PDI of SDS. B) PS and PDI of NSP.

Figure 1: PS and PDI of SDS and NSP.

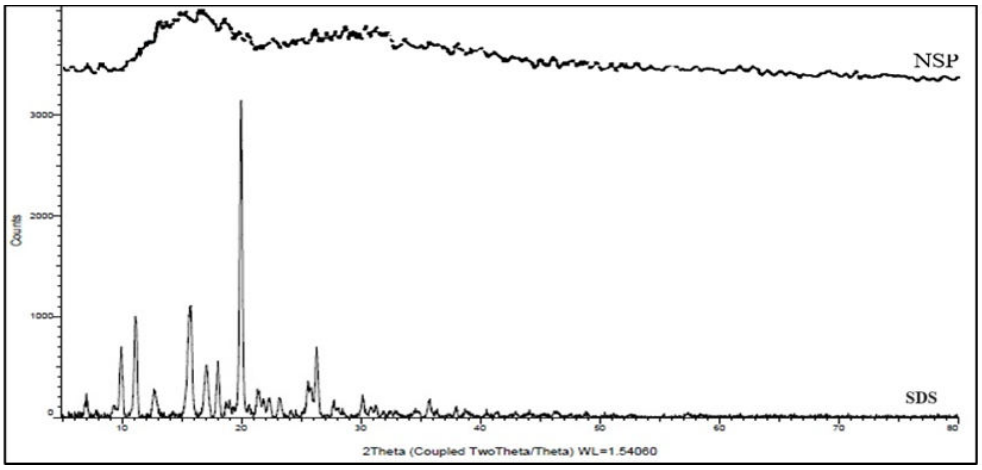
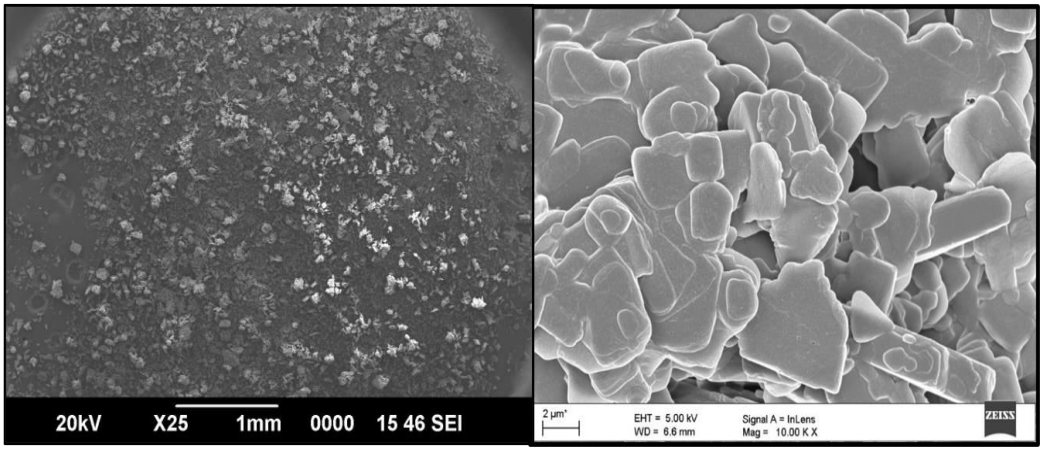


Figure 2: X-ray diffractogram of GFT and NSP.



A) SEM images of SDS-7 B) SEM image of NSP-6

Figure 3: SEM photomicrograph of both formulations.

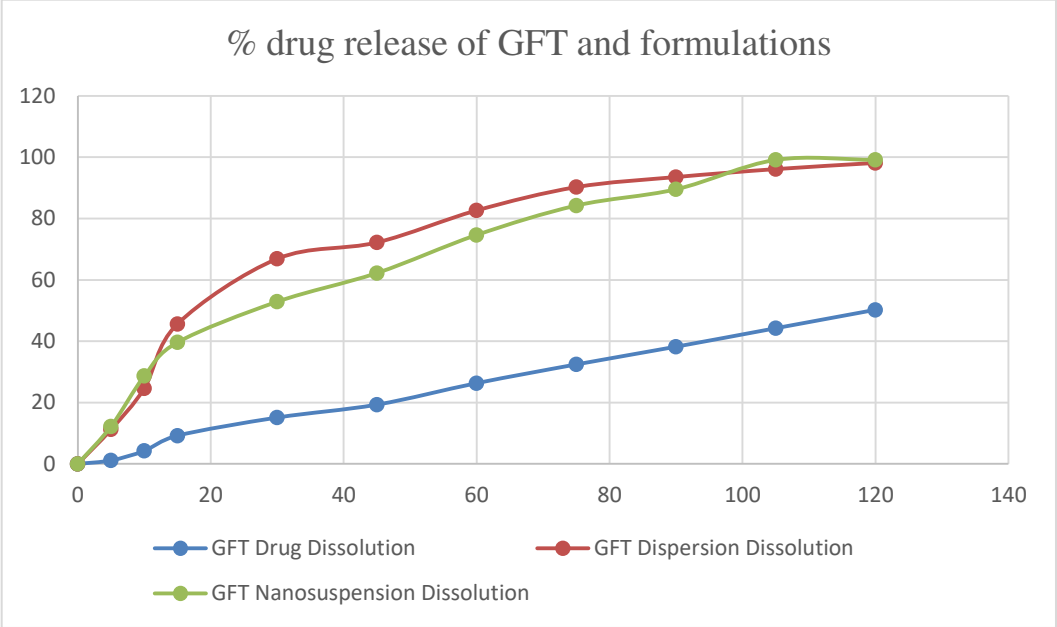


Figure 4: Cumulative % drug release of GFT pure drug, dispersion and nanosuspension.

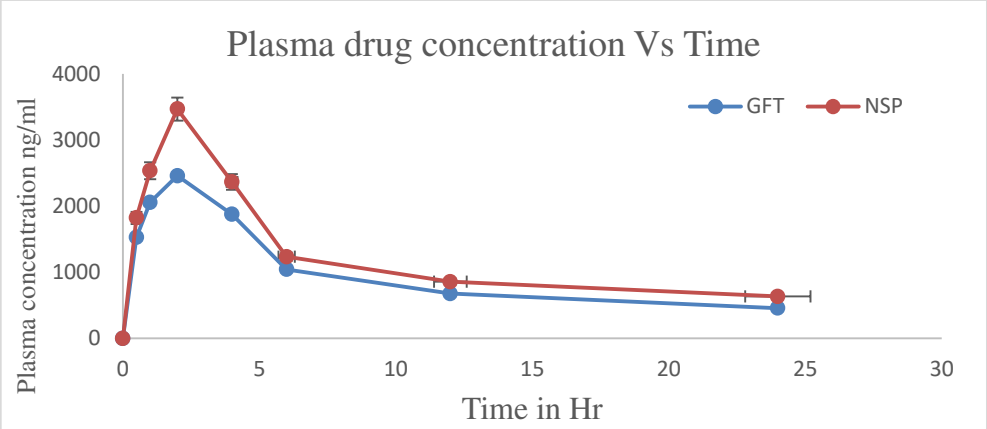


Figure 5: Plasma Drug Concentration vs. Time Profile of Plain GFT and NS6.

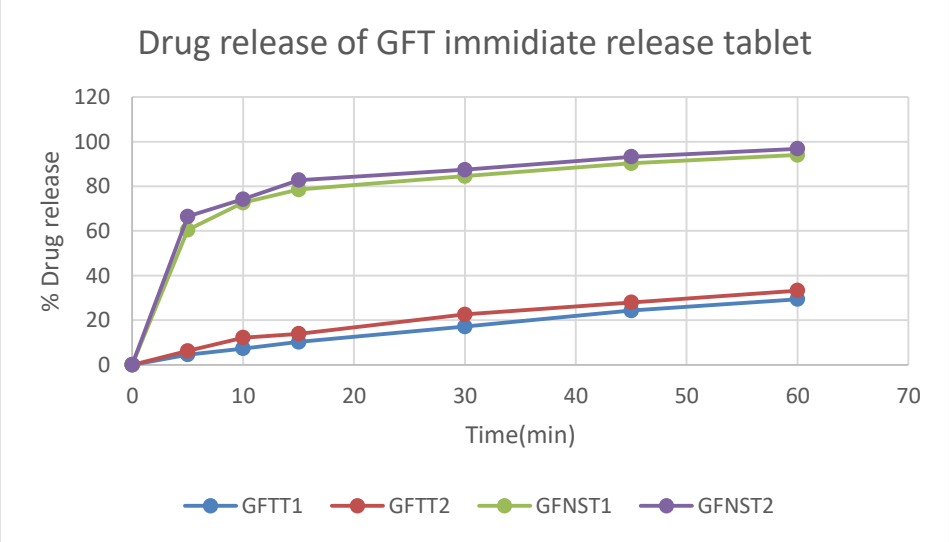


Figure 6: Dissolution profile of plain GFT and GFT nanosuspension tablets.

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