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Research

Formulation and in-Vitro Evaluation of Gefitinib Nano-Sponges

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Abstract

In this study, nano-sponges were prepared using the solvent evaporation technique and subsequently formulated into a gel form of Gefitinib. The Nano sponge formulations were prepared by solvent evaporation method employing β Cyclodextrin Ethyl Cellulose and poloxamer rate retarding polymers using PVA as a co polymer. The compatibility of the drug with formulation components was established by Fourier Transform Infra-Red (FTIR) spectroscopy. The surface morphology, production yield, and drug entrapment efficiency of nano-sponges were examined. The shape and surface morphology of the nano-sponges were examined using scanning electron microscopy. Scanning electron microscopy revealed the porous, spherical nature of the Nano-sponges. SEM photographs revealed the spherical nature of the nano-sponges in all variations; however, at higher ratios, drug crystals were observed on the nano-sponge surface. Increase in the drug/polymer ratio (1:1 to 1:2), which is in increasing order due to the increase in the concentration of polymer, but after a certain concentration, it was observed that as the ratio of drug to polymer was increased, the particle size decreased. The particle size was found in the range of 200-500 nm. The entrapment efficiency of different formulations is found in the range of 92.53 to 98.54%. The *in vitro* release studies revealed that the formulation with a higher concentration of penetration enhancer showed greater drug release.

Keywords: Gefitinib**,** β-Cyclodextrin, Nano-sponges Delivery System (NDS). Scanning Electron Microscopy (SEM), FTIR.

INTRODUCTION

In recent years, there has been considerable emphasis given to the development of novel nano sponge-based drug delivery systems to modify and control the release behavior of the drugs. By incorporation into a carrier system, it is possible to alter the therapeutic index and duration of action of the drugs. The ever-increasing interest among consumers regarding skin care and skin treatment products has been driven by the widespread use of ingredients like

α-hydroxy acids and vitamins in topical products, which can induce perceivable and demonstrable benefits, especially in aging or photo-damaged skin. Although quite useful, in many instances, these ingredients may cause irritancy; such irritancy can be perceived as burning, stinging, or redness, and is particularly produced in individuals with sensitive skin. Recognizing this problem, the formulators have attempted to deal with it in one of the two methods. They have reduced the concentration of such ingredients, but in the process, sacrificed efficacy. They have also modified the vehicle to make the product more emollient or skin-compatible.

Conventional formulations of topical drugs are intended to work on the outer layers of the skin. Typically, such products release their active ingredients upon application, producing a highly concentrated layer of active ingredients that is rapidly absorbed. Thus, the need for a system to maximize the amount of time that an active ingredient is present either on the skin surface or within the epidermis, while minimizing its transdermal penetration into the body.

Nano sponges are tiny, porous, polymeric microspheres, sponge-like structures typically 10-15 micrometres in size with cavities ranging from 5-30 micrometres capable of encapsulating a wide variety of drugs. These particles can carry both lipophilic and hydrophilic substances and improve the solubility of poorly water soluble molecules[1]. These are solid and can be formulated as oral, parenteral, topical, or inhalational dosage forms. Topical nano-sponge can be more patient compliant and provide sufficient patient benefits by reducing repeated doses and side effects[2]. The Nano sponge Delivery System (MDS) is a unique technology for the controlled release of topical agents. It is a novel class of hyper-crosslinked polymer-based colloidal structures consisting of solid nanoparticles, which are mostly used for prolonged topical administration. When applied to the skin, the nano sponge releases its active ingredient in time mode and in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over the counter (OTC) skin care, sunscreens, and prescription products.

Advantages [3-6]

1) This technology provides entrapment of active contents and protects them from degradation.
2) It provides improved stability, elegance, and formulation flexibility.
3) It is non-mutagenic, non-irritating, non-toxic, and Biodegradable.
5) It provides extended and predictable release, which is continuous action up to 12hr.
7) Therapeutic provides the onset of action. Formulation is cost-effective.
8) It can be used to mask unpleasant flavors and to convert liquid substances to solids, and has less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
10) Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.
11) Easy scale-up for commercial production.
12) The drug profiles can vary from fast, medium, to slow release in the case of dosing therapy.
13) Predictable release.

Disadvantages

1) Nano-sponges include only small molecules.
2) Depend only upon loading capacities.

Nano-sponges are prepared according to the criteria of the delivery system, polymer, nature of the drug, and solvents.

Nano sponges prepared from hyper-cross-linked β-cyclodextrins[7,8]

Prepared from β-cyclodextrins act as nanoporous materials, performing their work as carriers for drug delivery. Due to this, 3D networks are formed, which are roughly spherical structures about the size of a protein, having channels and pores in the internal part. Reacting cyclodextrin with a cross-linker such as di-isocyanates, diary carbonates, carbonyl di-imidazole's etc. Sponge size is controlled according to porosity, surface charge density for the attachment to different molecules. Nano sponges are synthesized in neutral or acidic form, depending on the cross-linker used. They consist of solid particles and are converted into crystalline form. The capacity of nano-sponges to encapsulate drugs having different structures and solubility. They are used to increase the aqueous solubility of poorly soluble drugs.

Emulsion solvent diffusion method[9]

In this method, two phases are used in different proportions of organic and aqueous(Ethyl cellulose and polyvinyl alcohol). The dispersed phase with ethyl cellulose and drug dissolved in dichloromethane (20 ml), and a definite amount of polyvinyl alcohol is added to 150 ml of aqueous continuous phase. Then, the mixture is stirred properly at 1000 rpm for 2hr. The required nano sponges were collected by filtration and kept for drying in an oven at 40ºc for 24 hours. Nano sponges, which are dried, were stored in desiccators for the removal of residual solvents.

Quasi-emulsion solvent diffusion[10,11]

The nano-sponges are prepared using polymer in different amounts. The inner phase is prepared using Eudragit RS 100 and added to a suitable solvent. The drug used was provided as a solution and dissolved under ultrasonication at 35 °C. This inner phase, added to the external phase containing PVA, acts as an emulsifying agent. The mixture is stirred at 1000-2000 rpm for 3 hours at room temperature and dried in an air-heated oven at 40 °C for 12 hours.

Evaluation of nano-sponges:

Particle size determination [9, 12]

The size of particles is maintained during polymerization to form the free-flowing powders with fine aesthetic attributes. The Particle size analysis of loaded and unloaded nano-sponges was performed by laser light diffractometry or Malvern Zeta Sizer. The cumulative graph is maintained or plotted as particle size against time to study the effect of particle size on drug release. Particles size greater than 30m impart a gritty feeling, and particles of sizes between 10 and 25 m are preferred and used in the final optical formulation.

Morphology and surface topography [13,14]

For the preparation of nano sponges in terms of morphology, they are coated with gold-palladium under an atmospheric oxygen at room temperature, and the surface structure is studied by scanning electron microscopy.

MATERIALS AND METHODS

Materials

Gefitinib -Pharma grade- B.M.R.Chemicals, Hyderabad, Polyvinyl alcohol (PVA), poloxamer- Colorcon, Goa, β cyclodextrin, Ethyl Cellulose- B.M.R.Chemicals, Hyderabad, Methanol and distilled water- Narmada Chemicals, Hyderabad.

Methodology

Preformulation studies

Before the development of nano-sponges dosage form, preformulation testing is the investigation of the physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the ratio development of a dosage form.

Solubility

Solubility of the Gefitinib was determined in different solvents like distilled water, 0.1 N HCl, and 6.8 pH buffers, and organic solvents like Ethanol & Methanol. Solubility studies were performed by taking an excess amount of the drug in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using Whatman's filter paper grade no. 41. The filtered solutions were analysed spectrophotometrically

Identification of Gefitinib

Determination of the UV spectrum of Gefitinib

Accurately weighed 10mg of Gefitinib was dissolved in 2-3 ml of methanol in a clean 10ml volumetric flask. The volume was made up to 10ml with 7.4pH buffer, so as to get a stock solution of 1000 µg/ml concentration. From the above stock solution, pipette out 1ml of the solution and make up the volume to 10ml using buffer to get the concentration of 100µg /ml. From stock solution-II, 1ml was pipetted out into a 10 mL volumetric flask. The volume was made up to 10ml using 7.4pH buffer to get a concentration of 10µg/ml. This solution was then scanned at 200-400nm in UV-Visible double beam spectrophotometer to attain the absorption maximum (λ-max).

Calibration curve

Preparation of Standard Calibration Curve of Gefitinib in pH 7.4

Preparation of Stock Solution10mg Gefitinib was dissolved in methanol in a 10ml volumetric flask. The volume was adjusted 7.4 pH buffer, which yields a stock solution concentration of 1000 µg/ml.

Preparation Standard Solution

1ml of stock solution was diluted to 10ml with pH 7.4 buffer in 10ml volumetric flask This gives a concentration of 10µg/ml. Aliquots of standard drug solutions were prepared and transferred into 10ml volumetric flasks and were diluted up to the mark with pH 7.4 buffer. This gives the final concentration of 2, 4, 6, 8, 10, and 12µg/ml Gefitinib, respectively. The absorbance of the solutions was measured at 332 nm against pH 7.4 as a blank using a UV-Vis spectrophotometer. The absorbance values at 332 nm were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Drug-Excipient Compatibility Studies

In the tablet dosage form, the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug-excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation studies must generate the needed information.

FT-IR Studies

Physical compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR). The FT-IR spectra obtained from Shimadzu Corporation, Tokyo, Japan, were utilized in determining any possible interaction between the pure drug and the excipients in the solid state. The potassium bromide pellets were prepared on a KBr press by grinding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely ground powder was then introduced into a stainless-steel die and compressed between polished steel anvils at a pressure of about $8t/in^2$. The spectra were recorded over the wave number of 4000 to $400cm^{-1}$.

Formulation design

Preparation of Nano sponges

Nano sponges using different proportions of β-cyclodextrin, poloxamer, Ethyl cellulose as rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by solvent evaporation method. Disperse phase consisting of Gefitinib(250gm) was dissolved in 20ml of solvent (methanol) and was slowly added to a definite amount of PVA in100ml of aqueous continuous phase, prepared by using a magnetic stirrer. The reaction mixture was stirred at 1000rpm for three hours on a magnetic stirrer for 2hours.The nano sponges formed were collected by filtration through Whatman filter paper and dried in oven at$50^{O}C$ for 2hours.The dried nano sponges were stored in vacuum desiccator to ensure the removal of residual solvent. The list of various formulations of gefitinib nano sponges are given in table 1.

Table: 1: Formulations of Gefitinib-loaded nano-sponges

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gefitinib	250	250	250	250	250	250	250	250	**250**
Poly Vinyl Alcohol	250	250	250	250	250	250	250	250	**250**
Poloxamer	250	500	750	--	--	--	--	--	**--**
Ethyl Cellulose	--	--	--	250	500	750	--	--	--
β-cyclodextrin	--	--	--	--	--	--	250	500	**750**
Methanol (ml)	10	10	10	10	10	10	10	10	**10**
Water (ml)	100	100	100	100	100	100	100	100	**100**

RESULTS AND DISCUSSION

Gefitinib Characterization

Solubility: Solubility of Gefitinib was carried out in different solvents like DMSO, methanol, Ethanol, 7.4 pH buffer, 0.1N HCL and 6.8 pH buffer. Solubility of the drug is higher in 7.4 pH phosphate buffer than7.4 pH buffer. In organic solvents, the solubility was found more in methanol than in ethanol. The solubility data is given in table 2, and the solubility graph is shown in figure 1.

Table 2: Solubility Studies of Gefitinib

Buffer	Solubility (mg/ml)
Ethanol	1.217
Methanol	1.485
0.1 N HCL	0.653
6.8 pH buffer	0.989
7.4pH buffer	1.241

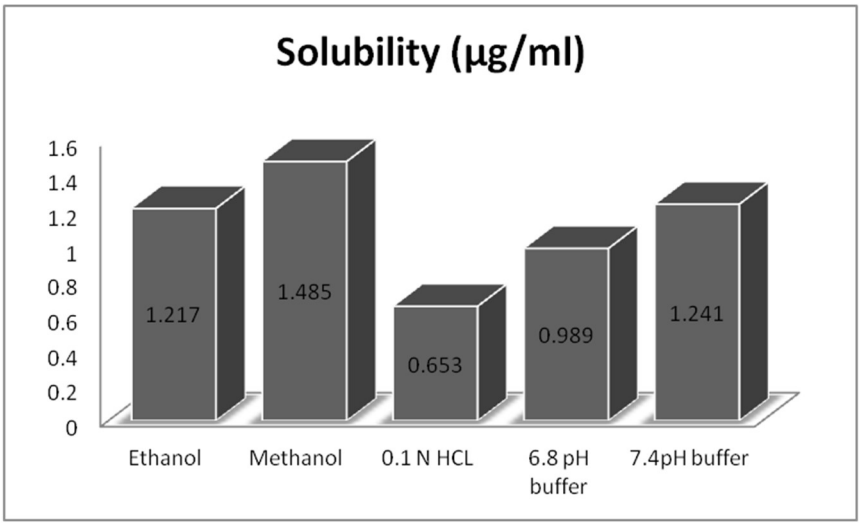

Fig 1: Solubility studies of Gefitinib

Determination of absorption maximum (λ max)

Determination of Gefitinib λ-max was done in 7.4 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate. The maximum absorbance of the Gefitinib was found to be 332 nm as shown in Fig 2. Hence, the wavelength of 332nm was selected for analysis of drug in dissolution media. The absorption spectrum is shown in figure 2.

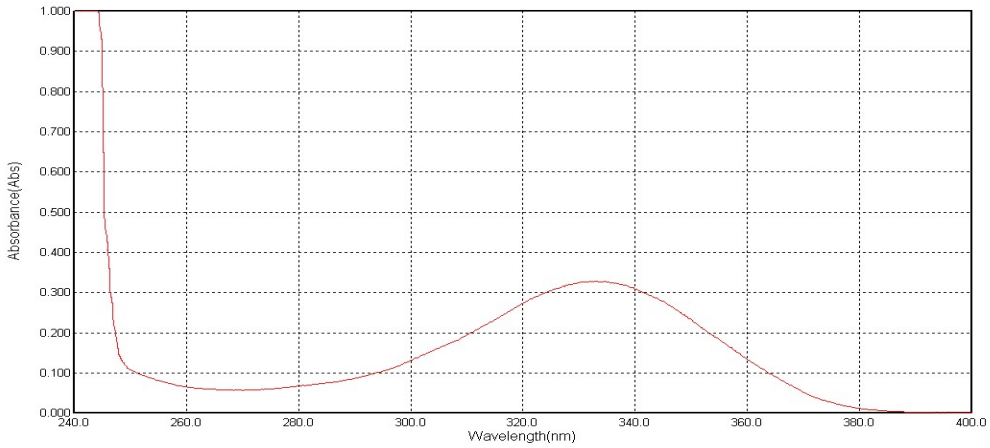

Fig 2: .λ-max in 7.4pH phosphate buffer

Calibration curve

The calibration curve was constructed to determine the linearity of drug concentration. The linearity was found to be in the range of 2-12µg/ml in 7.4pH phosphate buffer. The regression value was closer to 1, indicating the

method obeyed Beer-Lambert's law. The Linearity data is given in Table 3, and the calibration curve is shown in Figure.

Table 3: Calibration curve data of Gefitinib

Concentration (µg/ml)	Absorbance
0	0
2	0.146
4	0.292
6	0.431
8	0.559
10	0.687
12	0.833

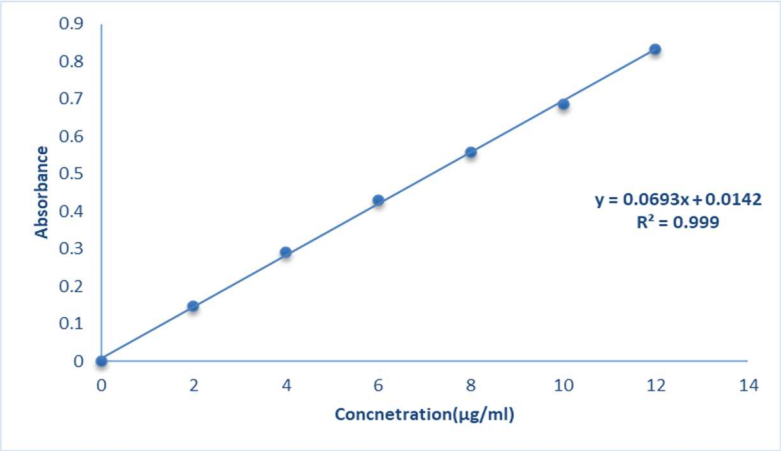

Fig 3: Calibration Curve of Gefitinib in 7.4 pH phosphate buffer

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing the spectra of the FT-IR of the Pure drug with those of various excipients used in the formulation. It was concluded that the functional groups present in the pure drug were present in the optimized formulation with fewer changes. From this, we can conclude that the drug and excipients have no interactions. The FT-IR Spectra of pure drug and drug-excipients are shown in figure 4 and 5.

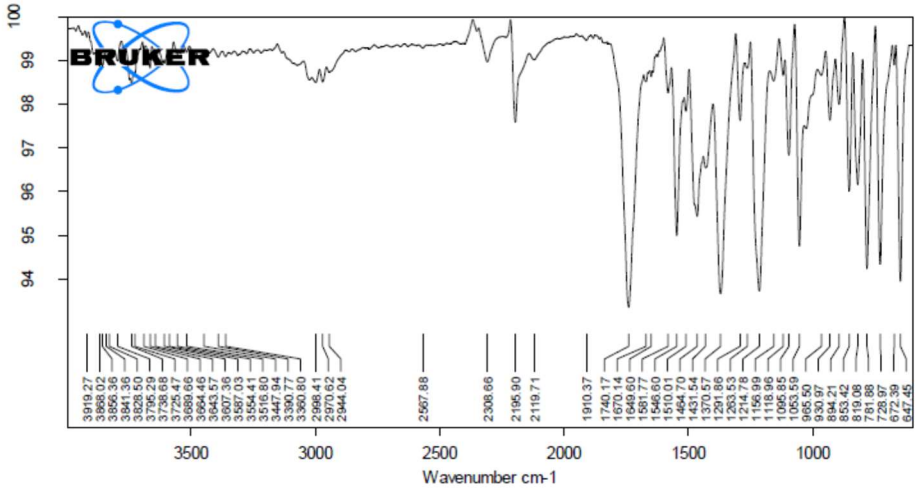

Fig 4: FTIR Spectra of Pure Drug

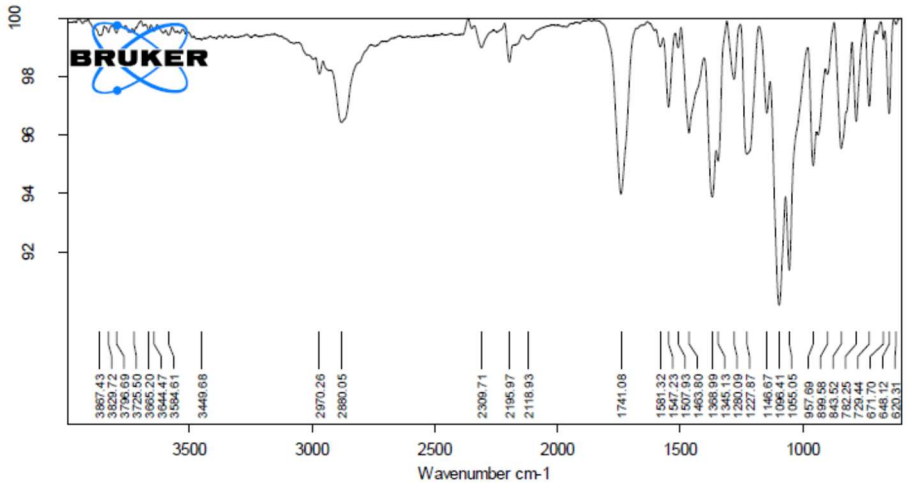

Fig 5: FTIR Spectra of drug and excipients

Particle size analysis

The particle size of the nano sponges was determined by optical microscopy, and the nano sponges were found to be uniform in size. The average particle size of all formulations ranges from 197 nm to 340 nm in increasing order due to the increase in the concentration of polymer, but after the certain concentration, it was observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be because in a high drug-to-polymer ratio, the amount of polymer available per Nano sponge was comparatively less. Probably in high drug-polymer ratios, fewer polymer amounts surround the drug, reducing the thickness of the polymer wall, and nano sponges with a smaller size were obtained. By performing particle size analysis, it is concluded that the formulation has a particle size that varies with the concentration of the polymer drug ratio. The mean particle size of formulations is given in Table 4.

Table 4: Mean Particle size of all formulations of Nano sponges

S.No	Formulation code	Mean Particle size (nm)
1	F1	260
2	F2	318
3	F3	325

4	F4	268
5	F5	198
6	F6	345
7	F7	260
8	F8	340
9	F9	200

Surface Morphology - scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) is useful for characterizing the morphology and size of microscopic specimens. Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared nano-sponges with particle sizes ranging from 10^{-10} - 10^{-12} nanometres. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. The Interaction of the electron beam with the specimen produces a variety of physical phenomena that, when detected, are used to form images and provide elemental information about the specimens.

It was observed that the nano-sponges were spherical and uniform with no drug crystals on the surface. The shape of the nano sponges affects the surface area per unit weight of spherical nano sponges. The irregular shape of the particles may affect the dissolution rate in the dissolution environment. The SEM photographs of the nano-sponges' structure of F9 are revealed in Figure 6.

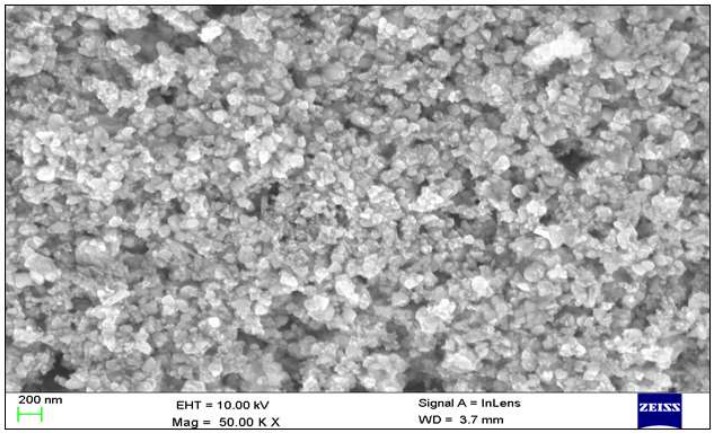

Fig 6: SEM photographs of Nano sponges' structure for optimized formulation (F9)

Entrapment efficiency

It is calculated to recognize the efficiency of any method; thus, it helps in the selection of an appropriate method of production. After the preparation of formulations, the Practical yield was calculated as the number of nano-sponges recovered from each preparation, with the sum of the starting material (Theoretical yield). It can be calculated using the following formula. The entrapment efficiency of formulations F1-F9 was found in the range of 92.83-98.54%. Among all the formulations, F9 shows a high entrapment efficiency of 98.54%. The percentage entrapment efficacy of all nano-sponges is given in Table 5.

$$\textbf{Entrapment efficiency} = \frac{\text{Practical yield}}{\text{Theoretical yield (drug + polymer)}} \times 100$$

Table 5: % Entrapment Efficiency of Nano sponges

S.No	Formulation code	Entrapment efficiency %
1	F1	92.53
2	F2	92.83
3	F3	94.48
4	F4	93.04
5	F5	95.16
6	F6	96.75

7	F7	95.15
8	F8	95.79
9	F9	98.54

In vitro dissolution studies of prepared Nano sponges

In vitro release studies were performed in triplicate using USP basket method at 50 rpm and 37±0.2°C in 900ml of phosphate buffer (pH 7.4). 10 mg of the formulated Nano sponges were used for each experiment. Samples were taken at appropriate time intervals for 1,2,3,4,5,6,7,8,9,10,11, & 12 hour. The samples were measured spectrophotometrically at 332 nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume. By comparing the above dissolution studies of formulations F1-F9. Maximum drug release was found in F9 formulation containing Drug: β-cyclodextrin in 1:2 ratio. So F9 formulation was taken as the optimized formulation, and drug release kinetics were performed for F9 formulation. The percentage of drug release of all formulations of gefitinib nano sponges is listed in table 6 &The % CDR profile of gefitinib Nanosponge formulations is shown in figure 7.

Table 6: Percentage of drug release of Nano-sponges (F1-F12)

Time	%CDR								
(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	28.27	26.03	19.79	27.63	25.78	18.94	25.09	26.34	11.48
2	35.65	28.84	27.13	35.42	38.12	24.38	34.47	34.75	17.64
3	49.24	35.17	35.48	56.76	49.05	29.79	43.07	41.12	21.27
4	61.58	49.75	42.61	65.98	57.72	35.63	51.63	49.28	28.69
5	67.16	62.18	48.82	71.39	66.34	41.78	59.27	56.18	35.89
6	79.34	76.78	57.68	81.24	75.65	48.69	65.39	67.34	39.75
7	85.18	81.69	63.79	89.45	82.67	55.12	74.15	75.25	47.89
8	97.66	90.27	75.39	94.61	89.67	66.79	81.36	81.84	61.75
9		95.84	81.32	98.42	91.95	78.42	93.09	87.63	78.29
10		98.26	89.41		98.36	86.24	99.02	92.65	81.42
11			98.83			90.23		98.12	89.79
12						97.32			**98.76**

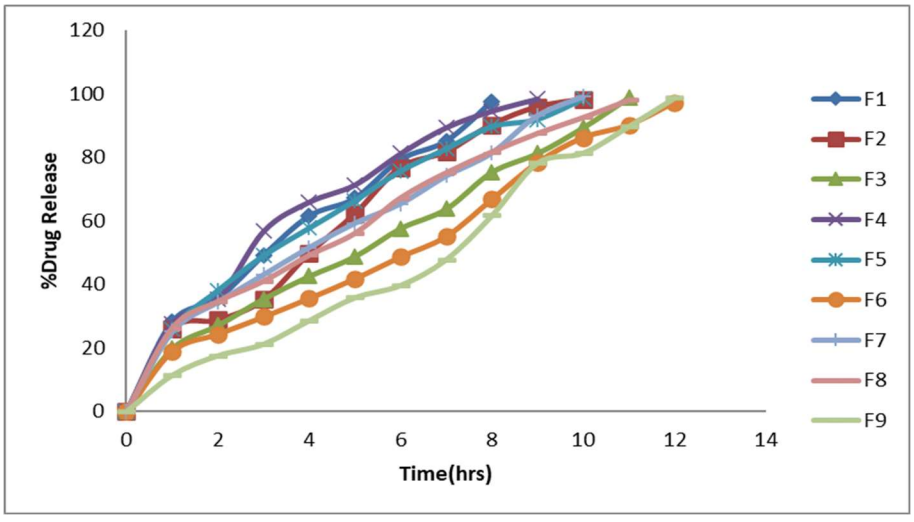

Fig 7: % CDR profile of gefitinib Nano sponges F1-F9

Drug Release Kinetics Studies

Regression values of F9

The optimized formulation **F9** has coefficient of determination (R^2) values of 0.981, 0.716, 0.874, and 0.811 for Zero order, First order, Higuchi, and Korsmeyer Peppas, respectively. A good linearity was observed with the first order, indicating the rate of drug release through the mode of diffusion, and further confirming the diffusion mechanism. data was fitted into the Korsmeyer Peppas equation, which showed linearity with an n value of 1.294 for optimized formulation. Thus, n value indicates the Non-Fickian diffusion. Thus, the release kinetics of the optimized formulation was best fitted into zero-order with non-Fickian diffusion. The Regression coefficient (r2) values of Gefitinib Nano sponges are given in Table 7.

Table 7: Regression coefficient (r2) values of Gefitinib Nano sponges

S.NO	Zero order	First order	Higuchi	Peppas
Code	R^2	R^2	R^2	R^2
F9	0.981	0.716	0.874	0.811

CONCLUSION

The Gefitinib Nanosponge was prepared by solvent evaporation method using β-cyclodextrin, Ethyl Cellulose and poloxamer as rate retarding polymers and PVA as co polymer using Methanol as a solvent. The prepared nano sponges were evaluated for its different parameters which revealed many interesting results for efficient preparation of the nano sponge. The formulation F9 has better results than other formulations. F9 have its particle size 200nm, entrapment efficiency 98.54%, Among the polymers used such as β-cyclodextrin, Ethyl Cellulose and poloxamer the drug polymers ratio of Gefitinib: β-cyclodextrin (1:2) ratio sustains the drug release up to 12 hours. The F9 drug release was found to be 98.76% in 12 hours, all these parameters are in optimized range for preparing a sustained release dosage form so showing itself as an optimized formulation in this project work. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the drug in thesenano sponge. SEM photographs revealed the spherical nature of the nanosponge in all variations. With the revealed results by different evaluation parameters, it is concluded that nanosponge drug delivery system has become highly competitive and rapidly evolving technology and more and more research are carrying out to optimize cost-effectiveness and efficacy of the therapy. The coefficient of determination (R^2) values of 0.981,0.716,0.874, and 0.811 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the zero order, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.294 for optimized formulation. Thus, n value indicates the non-fickian diffusion. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed first order drug release with non-fickian diffusion.

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