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Dastinib nano sponges - formulation development and evaluation

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Abstract

Nano sponges of Dasatinib were prepared by the solvent evaporation technique by employing Ethyl Cellulose, β Cyclodextrin, and poloxamer as rate retarding polymers using PVA as a copolymer. However, at higher ratios, drug crystals were observed on the Nano sponge surface. An increase in the drug/polymer ratio (1:3 to 1:1) is in increasing order due to the increase in the concentration of polymer. However, after a particular 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 250- 450 nm. The entrapment efficiency of different formulations was found in the range of 90.56 to 98.32%, by comparing the above dissolution studies of formulations F1-F9. Maximum drug release was found in the F5 formulation containing Drug: β-cyclodextrin in a 1:3 ratio. So F5 formulation was taken as the optimized formulation, and drug release kinetics were performed and which follows zero-order kinetics with super case II transport mechanism.

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Introduction

Nano sponges are novel class of hyper-crosslinked polymer-based colloidal structures consisting of solid nanoparticles with colloidal sizes and Nano sized cavities. They enhance stability, reduce side effects and modify drug release. The outer surface is typically porous, allowing sustain release of Drug. They are mostly use for topical drug delivery. Size range of Nano sponge is 50nm-100nm [1]. This technology is being used in cosmetics, over-the-counter skincare, sunscreens and prescribed drugs. Conventional formulation of topical drugs accumulates excessively in epidermis and dermis. Nano sponge prevents the accumulation of active ingredient in dermis and epidermis. Nano sponge system reduces the irritation of effective Drug without reduce their efficacy [2].

They can be used for targeting drugs to specific sites, prevent drug and protein degradation. These tiny sponges can circulate the body until they encounter the specific target site and stick on the surface and began to release the Drug in a controlled and predictable manner [3]. It is possible to control the size of the Nano sponge. To varying the portion of cross-linkers and polymers, the Nano sponge particles can be made larger or smaller4. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules [5]. Nano sponge technology offered entrapment of ingredients and believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Nano sponges are non-irritating, non-mutagenic, no allergenic and non-toxic [6]. Nano sponges are tiny mesh-like structures that used for the treatment of many diseases and this technology is five times more effective at delivering drugs for breast cancer than conventional methods. The Nano sponges are solid in nature and can formulated as oral, parenteral, topical or inhalational dosage forms. For oral administration, these may be dispersed in a matrix of excipients, diluents, lubricants and anticaking agents which is suitable for the preparation of tablets or capsules [6].

Nano sponges are porous, polymeric microspheres that are mostly used for prolonged topical administration. Nano sponges are designed to deliver a pharmaceutically

Active ingredient efficiently at the minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles.

The Nano sponge Delivery System (MDS) is a unique technology for the controlled release of topical agents and consist of microporous beads, typically 10-25 microns in diameter, loaded with an active agent. When applied to the skin, the Nano sponge releases its active ingredient on a time mode and also in response to other stimuli (rubbing, pH, etc.). MDS technology is being used currently in cosmetics, over -the – counter (OTC) skincare, sunscreens and prescription products.

Dasatinib is a BCS class II compounds that have poor solubility and good permeability are candidates for assessment of biopharmaceutical risks during dosage form design and development. Particularly, BCS class II weak bases that have a significant reduction in solubility ongoing from the gastric compartment to the intestine may show significant sensitivity to changes in gastrointestinal (GI) pH, transit times, and gastric emptying [7]

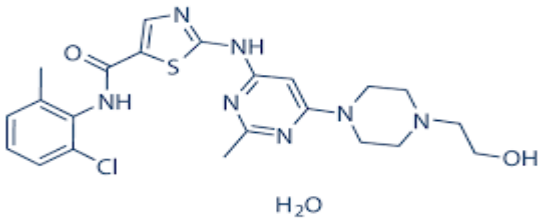

Figure: 1: chemical structure of Dasatinib

Experimental work

Materials and Methods

Dasatinib, β-Cyclodextrin, Polyvinyl alcohol (PVA), Poloxamer, Ethyl Cellulose, Dicloromethane, Water from B.M.R.Chemicals, Hyderabad and equipment and instruments like Electronic Weighing Balance from Shimadzu Corporation Tokyo, Japan, UV-Vis Spectrophotometer (T60) from PG Instrument, FTIR Spectrophotometer from Shimadzu Corporation Tokyo, Japan, Dissolution Apparatus from LAB India, Magnetic stirrer from Remi industries, Kerala.

Methodology

Pre-formulation studies [8-11]

Before the development of Nano sponge dosage form, it is essential that specific fundamental physical and chemical properties of the drug molecule alone and when combined with excipients are determined. This first learning phase is known as pre-formulation. The objective of the pre-formulation to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass-produced.

The goals of pre-formulation studies are:

- To evaluate the drug substance analytically and determine its necessary characteristics
- To establish its compatibility with different excipients.

Spectroscopic study

Identification of pure Drug

Solubility studies

The solubility of Dasatinib carried out in different solvents like- distilled 0.1N HCL, 7.4pH buffer and 6.8 pH buffer, and also in organic solvents like Ethanol, Dicloromethane. Solubility studies performed by taking an excess amount of Drug in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions filtered by using Whatman's filter paper grade no. 41. The filtered solutions were analyzed spectrophotometrically.

Determination of absorption maximum (λmax)

The wavelength at which maximum absorption of radiation takes place is called as λmax. This λmax is characteristic or unique for every substance and useful in identifying the substance. For accurate analytical work, it is important to determine the absorption maxima of the substance under study. Most drugs absorb radiation in the ultraviolet region (190-390nm), as they are aromatic or contain double bonds.

Accurately weighed 10mg Dasatinib separately was dissolved in 10 ml of Dicloromethane in a clean 10ml volumetric flask. The volume was made up to 10ml with the same which will give stock solution-I with concentration 1000µg/ml. From the stock solution-I, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 6.8pH buffer to obtain stock solution-II with a concentration 100µg/ml. From stock solution-II, 1ml was pipette out in 10ml volumetric flask. The volume was made up to 10ml using 6.8pH 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).

Construction of calibration curve using 6.8 pH buffer

Accurately weighed 10mg Dasatinib was dissolved in organic solvent taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 6.8 pH buffer, which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 6.8 pH buffer to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 6.8 pH buffer to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 315nm.

Construction of calibration curve using 0.1N HCL

Accurately weighed 10mg Dasatinib was dissolved in organic solvent taken in a clean 10ml volumetric flask. The volume was made up to 10ml with 0.1N HCl, which gives a concentration of 1000µg/ml. From this standard solution, 1ml was pipette out in 10ml volumetric flask and volume was made up to 10ml using 0.1N HCl to obtain a concentration of 100µg/ml. From the above stock solution, aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml each was transferred to a separate 10ml volumetric flask and solution was made up to 10ml using 0.1N HCl to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 315nm. Same procedure was repeated by using 6.8 pH phosphate buffer.

Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform – Infra-Red spectroscopy (FT-IR). The FT-IR spectra obtained from Bruker FT-IR Germany (Alpha T) was utilized in determining any possible interaction between the pure Drug and the excipients in the solid state. The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in2. The spectra were recorded over the wavenumber of 4000 to 400cm-1.

Preparation of Nano sponges [19, 11, 14, 16]

Table 1: Formulation table of Dasatinib loaded Nano sponges using solvent evaporation method

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dasatinib (g)	1	1	1	1	1	1	1	1	1
Ethyl Cellulose (g)	1	2	3	--	--	--	--	--	--
β-cyclodextrin (g)	--	--	--	1	2	1.5	--	--	--
Poloxamer (g)	--	--	--	--	--	--	1	2	3
PVA (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dimethyl sulfoxide	20	20	20	20	20	20	20	20	20
Water	100	100	100	100	100	100	100	100	100

Method of Preparation of Nanosponges by solvent Evaporation method:

Nanosponges using different proportions of β-cyclodextrin, Poloxamer, Ethylcellulose as rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by the solvent evaporation method. Disperse phase consisting of Dasatinib and requisite quantity of PVA dissolved in 10 ml solvent (Dimethyl sulfoxide) was slowly added to a definite amount of PVA in 100ml of a continuous aqueous phase, prepared by using a magnetic stirrer. The reaction mixture was stirred at 1000 RPM on a magnetic stirrer for 2hours and kept on hot plate upto complete removal of organic solvent from the formulation. The nanosponges formed were collected by filtration through whatman filter paper and dried.

Evaluation parameters of Nano sponges [11-19]

The Nano sponges was evaluated for various parameters:-

Entrapment efficiency

The 100mg of the Dasatinib weight equivalent Nano sponges was analysed by dissolving the sample in 10ml of Dimethyl sulfoxide. After the Drug was dissolved 10ml of clear layer of dissolved Drug is taken. Thereafter the amount of Drug in the water phase was detected by a UV-Spectrophotometric method at 315nm (U.V Spectrophotometer). The concentration of the Drug is determined with the help of the calibration curve. The amount of Drug inside the particles was calculated by subtracting the amount of Drug in the aqueous phase of the suspension from the total amount of the Drug in the nanoparticle suspension. The entrapment efficiency (%) of Drug was calculated by the following equation.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of Drug in Nano sponge}}{\text{Mass of Drug used in the formulation}} \times 100$$

Scanning electron microscopy

The morphological features of prepared nanospongess are observed by scanning electron microscopy at different magnifications.

Dissolution study

Dissolution Parameters

Medium: 900ml, 0.1N HCL for 2hrs and 6.8pH buffer for 10hrs.

Apparatus: Basket (USP-I)

RPM: 50

Temperature: 37° C±0.5

Time Points: 1, 2, 3,4,5,6,7,8,9,10,11,12, hr

Procedure

For the oral dosage forms the in vitro dissolution study must be conducted in the dissolution medium which simulate the in-vivo conditions (actual physiological conditions). The in vitro drug release studies for the prepared formulation were conducted for a period of 12 hrs using an Electro lab model dissolution tester USP Type-1 apparatus (rotating basket) set at 50 RPM and a temperature of 37± 0.5°C weight equivalent to 100mg of Dasatinib nanosponge was filled in capsule and kept in basket apparatus and placed in the 900ml of the medium. At specified intervals 5ml samples were withdrawn from the

Dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample solution was analysed at 315nm for the presence of model Drug, using a UV-visible spectrophotometer.

Modelling of Dissolution Profile [20-21]

In the present study, data of the in vitro release were fitted to different equations and kinetic models to explain the release kinetics of Dasatinib from the matrix tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

Kinetic Studies: Mathematical models [21]

Results & Discussions

Solubility studies

The solubility studies we can say solubility of the Drug is more in 6.8pH buffer than the other buffers. In organic solvents, the solubility was found more in Dimethyl sulfoxide.

Table 2: Solubility Studies of Dasatinib

Solvents	Solubility (µg/ml)
0.1 N HCL	0.367
6.8 pH buffer	0.689
7.4pH buffer	0.542
Ethanol	1.239
Methanol	1.578
Dimethyl sulfoxide	3.294

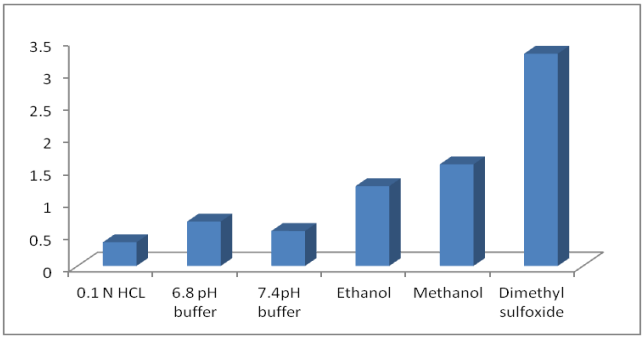

Fig 2: Solubility Studies of Dasatinib

Drug excipient compatibility

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of Pure Drug with that of various excipients used in the formulation The characteristic absorption peaks of Drug and excipients were obtained as shown above and as they were in official limits (±100 cm^{-1}) the Drug is compatible with excipients. Drug with that of various excipients used in the formulation.

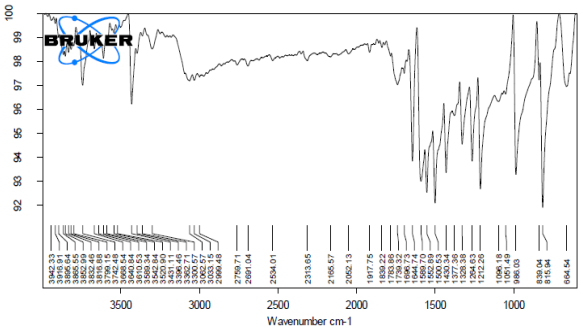

Fig. 3 : FTIR Spectra of Pure Drug

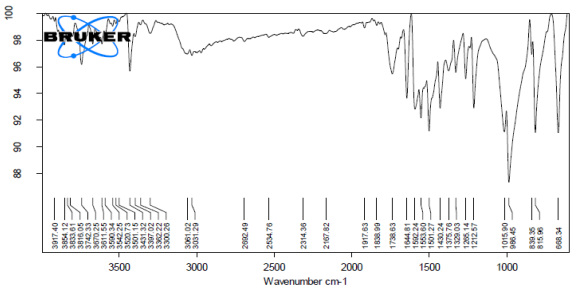

Fig. 4 : FTIR Spectra of Optimized Formulation

Determination of absorption maximum (λmax)

Determination of Dasatinib λ-max was done in 6.8 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate. The maximum absorbance of the Dasatinib in pH 6.8 buffer was found to be 318nm.

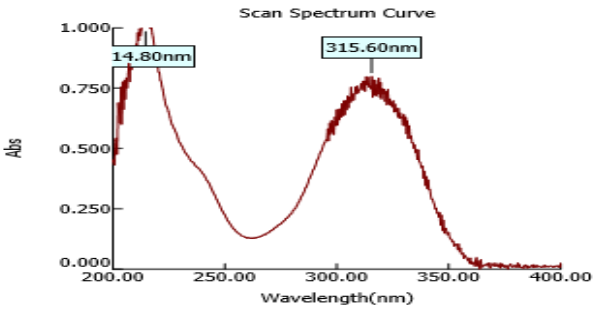

Fig. 5 : λ-max in 6.8 phosphate buffer

The linearity was found to be in the range of 2-12µg/ml in 0.1N HCL and 6.8 phosphate buffer. The regression value was closer to 1 indicating the method obeyed Beer-lambert's law.

Calibration curve

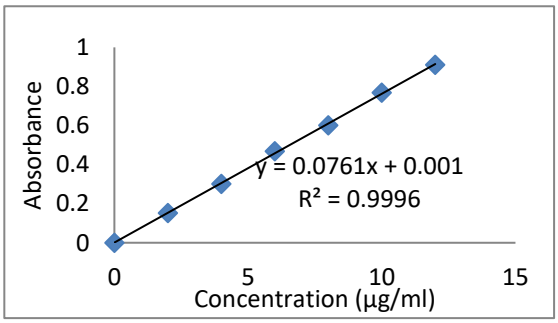

Fig: 6 Calibration curve data of Dasatinib in 0.1N HCL

Table 4: Calibration curve data of Dasatinib in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.103
4	0.196
6	0.308
8	0.412
10	0.529
12	0.641

Table 5: Calibration curve of Dasatinib in 6.8 pH buffer:

Concentration (µg/ml)	Absorbance
0	0
2	0.153
4	0.302
6	0.469
8	0.601
10	0.769
12	0.911

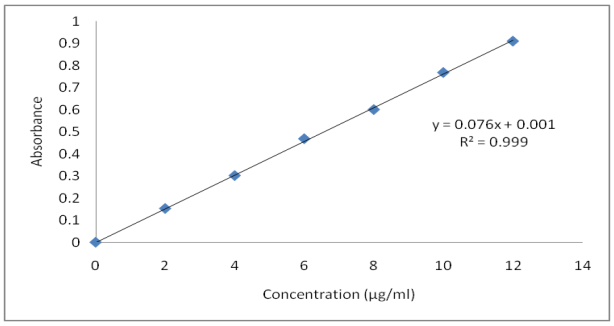

Fig 7: Calibration curve of Dasatinib in 6.8 pH buffer

A) Particle size analysis of Nano sponges

The particle size of the Nano sponge was determined by optical microscopy and the Nano sponges were found to be uniform in size. The average particle size of all formulations was found below 500nm which is in increasing order due to the increase in the concentration of polymer but after certain concentration it was observed that as the ratio of Drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high Drug to polymer ratio, the amount of polymer available per Nano sponge was comparatively less. Probably in high drug-polymer ratios less polymer amounts surround the Drug and reducing the thickness of polymer wall and Nano sponges with smaller size were obtained. By performing the particle size analysis, it is concluded that the formulation has the particle size varies with the concentration of polymer drug ratio.

B) Morphology determination by scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) was used to determine the Morphology of the prepared Nano sponges. SEM is useful for characterizing the morphology and size of microscopic specimens with particle size as low as 10 -10 to 10 -12 grams. The sample was placed in an evacuated chamber and scanned in a controlled pattern by an electron beam. 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.

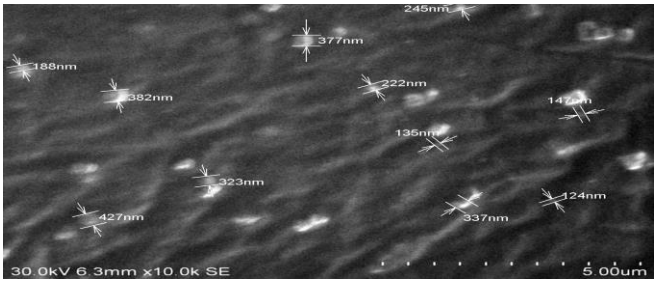

Fig: 8 Nano sponges structure optimized formulation (F6)

The morphology of the Nano sponges prepared by emulsion solvent evaporation method were investigated by SEM. The representative SEM photographs of the Nano sponges are shown in Fig... 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 and surface area per unit weight of spherical Nano sponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment. The spongy and porous nature of the Nano sponges can be seen in figures.

Entrapment efficiency

It is calculated to know about the efficiency of any method, thus it helps in selection of appropriate method of production. After the preparation of formulations the Practical yield was calculated as Nano sponges recovered from each preparation in relation to the sum of starting material (Theoretical yield). It can be calculated using following formula.

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

Table: 6 Entrapment Efficiency F1-F9

Formulation code	% Entrapment Efficiency
F1	95.67
F2	92.48
F3	93.76
F4	98.12
F5	99.12
F6	96.24
F7	95.36
F8	92.17
F9	91.56

The entrapment efficiency of formulation F1-F9 was found to be in the range of 91.56 to 99.12%.

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 0.1N HCl for 2hrs and remaining hours in phosphate buffer (pH 6.8). 10 mg of the formulated Nano sponges is 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 315nm. Fresh dissolution medium was replenished each time when sample is withdrawn to compensate the volume.

Table:7 Percentage of drug release of Nano sponges (F1-F9)

Time (hours)	%CDR								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	36.19	32.8	24.08	22.75	19.82	16.83	42.16	35.76	32.19
2	48.53	39.42	29.852	39.46	23.45	20.46	52.08	41.63	39.75
3	56.32	46.18	36.46	46.25	29.76	29.73	63.18	52.37	46.07
4	69.35	52.76	51.82	56.83	36.18	36.95	69.73	61.73	53.18
5	75.28	62.83	59.37	63.18	42.76	49.36	75.31	69.72	59.62
6	86.17	69.36	64.13	72.46	53.86	55.31	83.46	76.31	63.48
7	92.43	75.43	69.31	80.76	61.79	62.34	91.06	82.61	72.43
8	97.56	81.36	76.09	89.43	75.36	75.16	95.18	89.62	81.63
9		89.25	81.34	96.18	86.19	80.43		94.05	86.13
10		99.43	88.95		95.37	89.72			92.51
11			95.24			95.36			97.13
12						98.16			

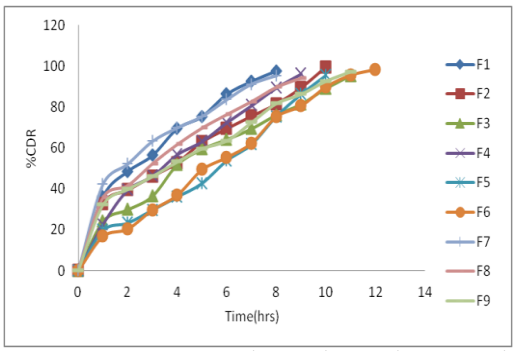

Fig 9 : Percentage cumulative drug release graph F1-F9

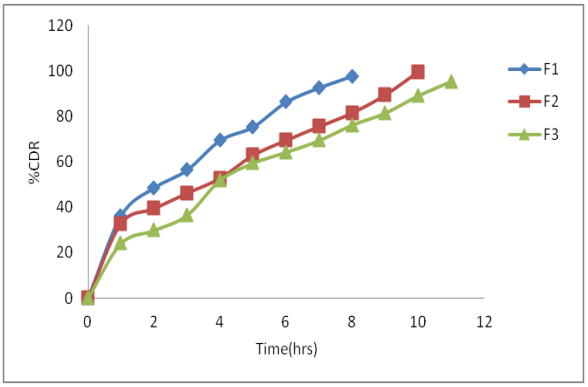

Fig 10: Percentage of Cumulative drug release graph F1-F3

From the above invitro dissolution studies it was observed that the formulations containing ethyl cellulose with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3). F1 Formulations shows maximum drug release at the end of 8th hour. Whereas F2 formulation shows maximum drug release at the end of 10hr. while F3 formulation shows maximum drug release at the end of 11hr.

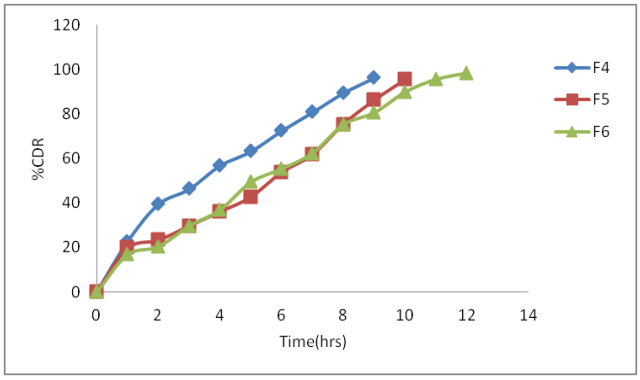

Fig 11 : Percentage of Cumulative drug release graph F4-F6

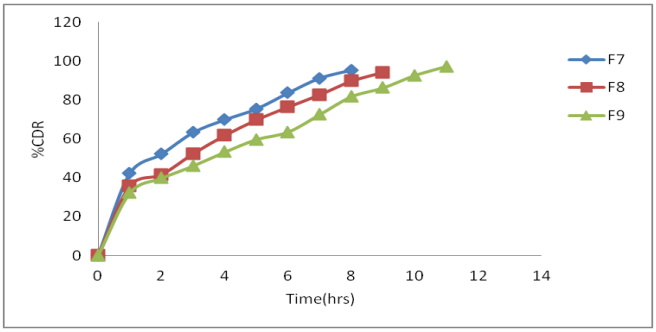

Fig 12 : Percentage of Cumulative drug release graph F7-F9

From the above invitro dissolution studies it was observed that the formulations containing β cyclodextrin with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3). F4 Formulations shows maximum drug release at the end of 9 hour. Whereas F5 formulation shows maximum drug release at the end of 10hr. while F6 formulation shows maximum drug release at the end of 12hr. From the above invitro dissolution studies it was observed that the formulations containing poloxamer with PVA using solvent evaporation method with drug in (1:1, 1:2, 1:3). F7 Formulations shows maximum drug release at the end of 8

hour. Whereas F8 formulation shows maximum drug release at the end of 9hr. while F9 formulation shows maximum drug release at the end of 11hr. By comparing the above dissolution studies of formulations F1-F9. Maximum drug release was found in F6 formulation containing Drug: β-cyclodextrin in 1:3 ratio. So F5 formulation was taken as the optimized formulation, and drug release kinetics were performed for F5 formulation.

Table 8 : Regression values formforamualtion F5

Formulation Code	Zero order	First order	Higuchi	Peppas	Peppas
	R^2	R^2	R^2	R^2	n
F6	0.991	0.852	0.943	0.748	1.244

Discussion

The optimized formulation **F5** has coefficient of determination (R^2) values of 0.991, 0.852, 0.943, 0.748 for Zero order, First order, Higuchi, Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.244 for optimized formulation. Thus n value indicates the supercase II transport mechanism.

Summary & Conclusion

The Nano sponge was prepared by solvent evaporation method using ethyl cellulose, βcyclodextrin and Poloxamer, as rate retarding polymers, PVA and DMSO (Dimethyl sulfoxide) as crosslinking agents. The prepared Nano sponges were evaluated for its different parameters which revealed many interesting results for efficient preparation of the Nano sponge. FTIR spectroscopy analyses indicated the chemically stable, amorphous nature of the Drug in these Nano sponge. SEM photographs revealed the spherical nature of the Nano sponge in all variations. With the revealed results by different evaluation parameters, it is concluded that Nano sponge 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 formulation F6 has better results than other 9 formulations. F6 have its particle size 200nm, entrapment efficiency 96.24%, drug release 98.16 % in 12 hours, the optimized formulation **F5** has coefficient of determination (R^2) values of 0.991, 0.852, 0.943, 0.748 for Zero order, First order, Higuchi, Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, the slope of the regression line from the Higuchi plot indicates the rate of drug release through the mode of diffusion and to further confirm the diffusion mechanism, data was fitted into the Korsmeyer Peppas equation which showed linearity with n value of 1.244 for optimized formulation. Thus n value indicates the supercase II transport mechanism.

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