World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

PREPARATION AND EVALUATION OF LESINURAD NANOSPONGES BY USING SOLVENT EVAPORATION METHOD

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Received: 04-11-2024 / Revised Accepted: 18-11-2024 / Published: 05-12-2024

ABSTRACT:
In this study Lesinurad Nanosponges were prepared by the solvent evaporation technique. The Nanosponges formulations were prepared by solvent evaporation method employing HPMC K4, Carbopol 934, Sodium Alginate 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, percentage yield, and drug entrapment efficiency of Nanosponges were examined. Shape and surface morphology of the Nano sponges were examined using scanning electron microscopy. Scanning electron microscopy revealed the porous, spherical nature of the Nanosponges. 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 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. The particle size was found in the range of 500 to 680 nm. The entrapment efficiency of different formulations was found in the range of 57.16±1.35% to 78.12±1.33%. The in vitro release studies revealed that the formulation with higher concentration of penetration enhancer showed greater drug release.
Keywords: Lesinurad, Sodium Alginate, Scanning Electron Microscopy (SEM), FTIR.

INTRODUCTION

Lesinurad is a uricosuric agent in development for the chronic management of gout and hyperuricemia. It was discovered by Ardea Biosciences as a major metabolite of a candidate nonnucleoside reverse transcriptase inhibitor, RDEA809, and was found to be the compound responsible for the urate-lowering effect observed in their study subjects. Lesinurad has been demonstrated to inhibit both the URAT-1 and OAT4 transporters in the renal tubule[1]

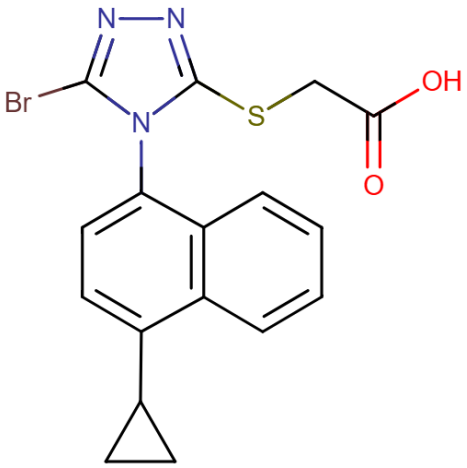

Figure.1 Structure of Lesinurad[2]

Nanosponge is a novel approach which offers controlled drug delivery for topical use. Nanosponge is an emerging technology for topical drug delivery. Nanosponge drug delivery system is employed for the

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How to Cite this Article Dr. D. Nirmala. Preparation and Evaluation of Lesinurad Nanosponges by Using Solvent Evaporation Method, World J Pharm Sci 2023; 12(04): 84-94; https://doi.org/10.54037/WJPS.2022.100905.

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improvement of performance of topically applied drugs. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs.[3-12] These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects, improved stability, increased elegance and enhanced formulation flexibility. Nanosponges are nonirritating, non-mutagenic, non-allergenic and nontoxic. Nanosponges are made up of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules. Nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core.

MATERIALS & METHODS USED: Lesinurad API was procured from Manus Aktteva Biopharma LLP and Poly Vinyl Alcohol, HPMC K4 were procured from COLORCON GOA, Carbopol 934, Sodium Alginate were procured from B.M.R.Chemicals, Hyderabad and Dichloromethane, Distilled Water(ml) were procured from Narmada Chemicals, Hyderabad.

Method of Preparation of Nanosponges:[13-18]

Nanosponges using different proportions of HPMC K4, Carbopol 934, Sodium Alginate as rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by solvent evaporation method. Disperse phase consisting of Lesinurad(200gm) was dissolved in 20ml solvent (Dichloromethane) and was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using magnetic stirrer. The reaction mixture was stirred at 1000 rpm for three hours on a magnetic stirrer for 2hours. The nanosponges formed were collected by filtration through whatman filter paper and dried in oven at 50oC for 2 hours. The dried nano sponges were stored in vaccum desicator to ensure the removal of residual solvent.

Table No.1 Formulation Table

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lesinurad	200	200	200	200	200	200	200	200	200	200	200	200
Poly Vinyl Alcohol	400	400	400	400	400	400	400	400	400	400	400	400
HPMC K4	100	200	300	400	--	--	--	--	--	--	--	--
Carbopol 934	--	--	--	--	100	200	300	400	--	--	--	--
Sodium Alginate	--	--	--	--	--	--	--	--	100	200	300	400
Dichloromethane (ml)	20	20	20	20	20	20	20	20	20	20	20	20
Water (ml)	100	100	100	100	100	100	100	100	100	100	100	100

Entrapment efficiency:[19-21]The 200mg of the Lesinurad weight equivalent nano sponge was analyzed by dissolving the sample in 10ml of distilled water. 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 290 nm (U.V Spectrophotometer, systronics). The test was repeated with another nanoparticulate sample. The amount of the drug in the suspension was analyzed by centrifugation at 500rpm for 5 mins and by measuring the concentration of the drug in the clear supernatant layer by the UV-spectrophotometric method. The concentration of the drug is determined with the help of 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.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of drug in nanosponge}}{\text{Mass of drug used in formulation}} \times 100$$

Percentage yield: The Lesinurad nanosponges obtained after drying was weighed. Percentage yield value was calculated as follows:

$$\% \text{ yield} = \frac{\text{Weight of nanosponges}}{\text{Total solids weight}} \times 100$$

Scanning electron microscopy: The morphological features of prepared nanospongess are observed by scanning

electron microscopy at different magnifications.

Particle size: Average particle size and shape of the formulated nanospongess was determined by using Malvern Zetasizer ZS using water as dispersions medium. The sample was scanned for determination of particle size.

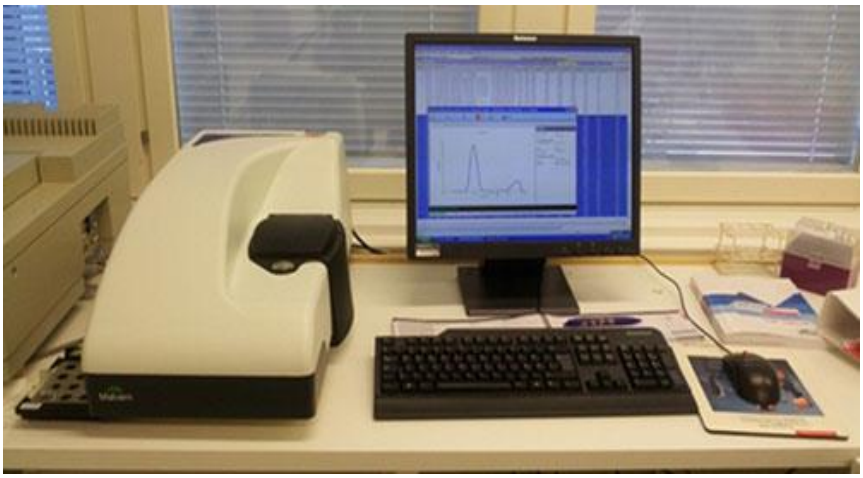

Figure.2 Photography representation of Malvern zetasizer used for finding particle size analysis

Dissolution Parameters

Medium : 900ml, 0.1 N HCl buffer for 12hrs.
Apparatus : Basket (USP-I)
RPM : 50
Temperature : 37º 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 200mg of Lesinurad nano sponge 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 analyzed at 290 nm for the presence of model drug, using a UV-visible spectrophotometer.

Modelling of Dissolution Profile

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

Kinetic Studies: Mathematical models:[22,23]

Different release kinetic equations (zero-order, first-order, Higuchi's equation and Korsmeyer-peppas equation) were applied to interpret the release rate of the drug from matrix systems for the optimized formulation. The best fit with higher correlation (r2) was calculated.

Zero-order model:

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be representedby the equation

$$Qt = Q0 + K0t$$

First Order Model:

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.

Release behavior generally follows the following first order equation:

$$Log\ C = Log\ C_o - kt/2.303$$

Higuchi model: The first example of a mathematical model aimed to describe drug release from a system was proposed by Higuchi in 1961. Initially conceived for planar systems, it was then sustained to different geometrics and porous systems. This model is based on the hypothesis that

$$Q = K_H - t^{1/2}$$

Korsmeyer-Peppas model: Korsmeyer et al.(1983) derived a simple relationshipwhich described drug release from a polymeric system equation. To find out the mechanism of drug release, first60% drug release data were fitted in Korsmeyer-Peppas model,

$$Mt / M\infty = Kt^n$$

RESULTS AND DISCUSSIONS

Solubility: Solubility of Lesinurad was carried out in different solvents like-, Dichloromethane, Ethanol, 7.4pH phosphate buffer, 0.1N HCL and 6.8 pH phosphate buffer.

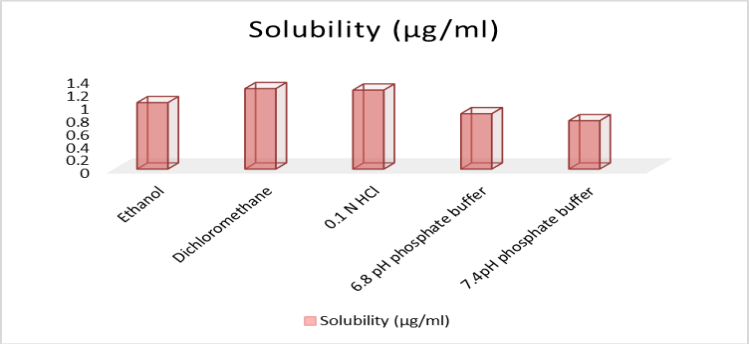

Figure.3 Solubility studies of Lesinurad

Discussion:

From the above obtained solubility studies we can say solubility of the drug is more in 0.1 N HCl buffer than the other buffers. In organic solvents the solubility was found more in Dichloromethane than other organic solvents.

Determination of absorption maximum (λmax): Determination of Lesinurad λ-max was done in 0.1 N HCL buffer for accurate quantitative assessment of drug dissolution rate.

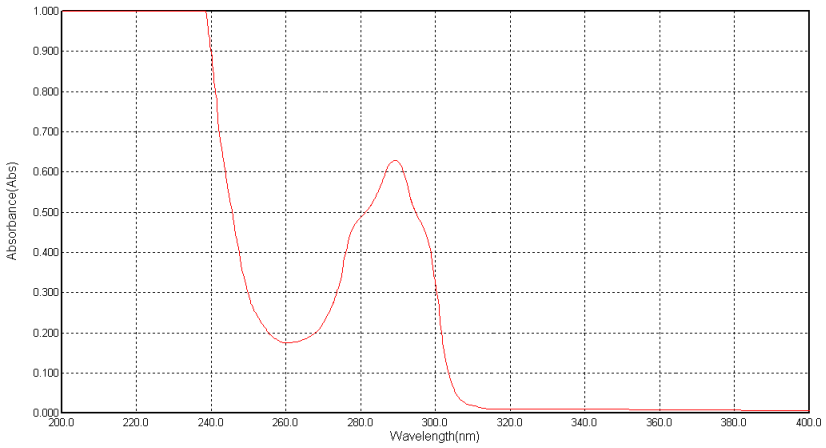

Figure.4 λ-max in 0.1 N HCl

Discussion: The maximum absorbance of the Lesinurad in 0.1 N HCl buffer was found to be 290 nm as shown in Fig. Hence, the wavelength of 290 nm was selected for analysis of drug in dissolution media.

Calibration curve:

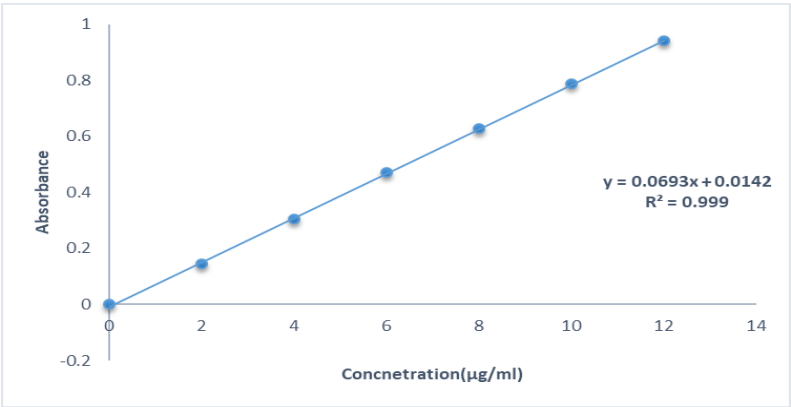

Figure.5 Calibration Curve of Lesinurad in 0.1 N HCl buffer

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

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.

Pure:

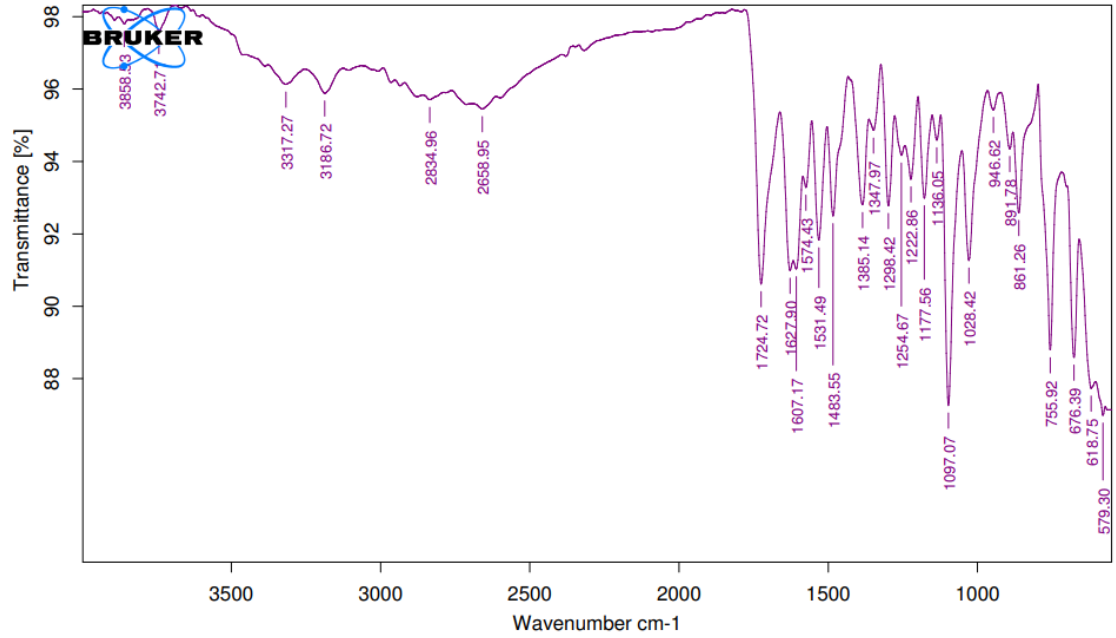

Figure.6 FTIR Spectra of Pure Drug

Optimized Formulation

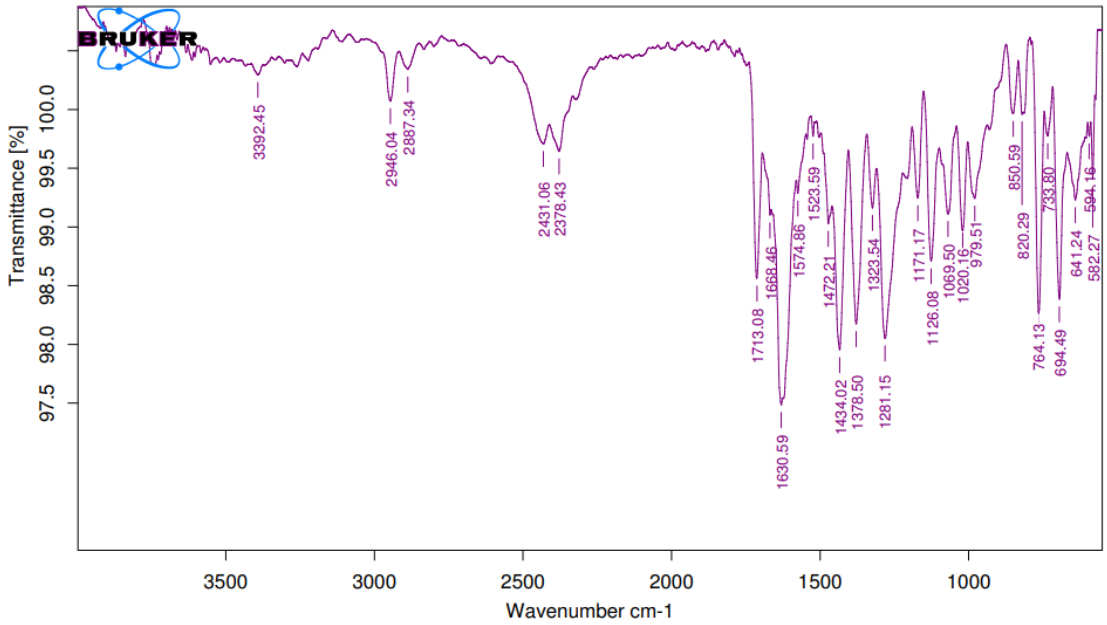

Figure.7 FTIR Spectra of drug and excipients

Discussion: -

From the compatibility studies it was concluded that the functional groups that were presented in the pure drug were present in the optimized formulation with very minute changes, from this we can concluded that the drug and excipients have no interactions.

Entrapment efficiency:

Table No.2 % Entrapment Efficiency of Nano sponges

Formulation code	Entrapment efficiency %
F1	57.16±1.35
F2	62.38±1.45
F3	65.97±1.12
F4	69.45±1.39
F5	59.02±1.45
F6	65.45±1.16
F7	70.63±1.20
F8	73.95±1.75
F9	64.45±1.36
F10	69.38±2.71
F11	74.75±1.12
F12	78.12±1.33

Discussion: The entrapment efficiency of formulation F1-F12 was found in the range of 57.16±1.35% to 78.12±1.33%. Among all the formulations F12 shows high entrapment efficiency of 78.12±1.33%.

Percentage yield

Table No.3 Percentage yield

Formulation code	Percentage yield
F1	87.46±1.12
F2	89.29±1.24
F3	92.06±1.37
F4	93.37±1.45
F5	89.16±1.67
F6	93.98±1.41
F7	95.42±1.20
F8	96.21±1.16
F9	92.36±1.24
F10	95.75±1.43
F11	96.81±1.85
F12	99.16±1.15

Discussion: The Percentage yield of formulation F1-F12 was found in the range of 87.46±1.12% to 99.16±1.15%. Among all the formulations F12 shows Percentage yield of 99.16±1.15%.

Morphology determination by scanning electron microscopy (SEM):

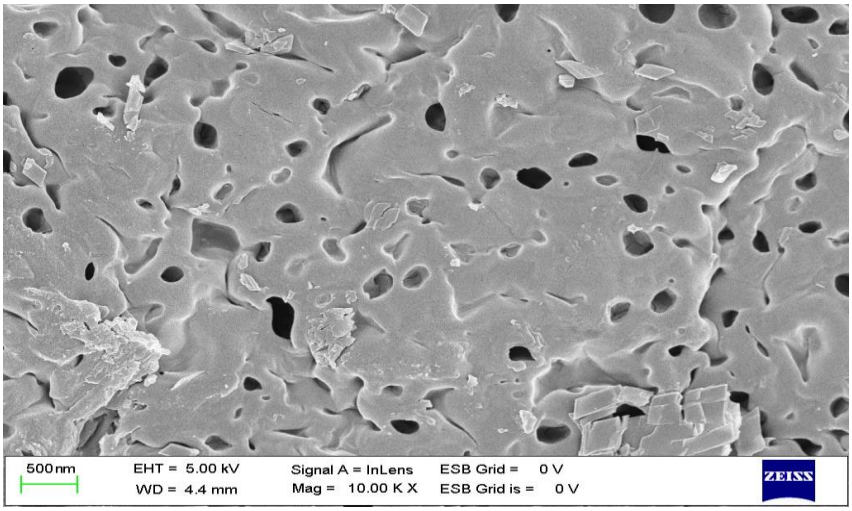

Figure.8 SEM

Discussion:

The surface morphology of the Lesinurad nanosponge was studied by SEM. SEM photographs of the optimized formulation. Surface morphology of the Lesinurad nanosponge was found to be rigid nature.

Particle size analysis of Nano sponges:

Discussion:

As the ratio of polymer was increased, the mean particle size of Lesinurad nanosponges had also decreased. The significant decrease may be due to the increase in the viscosity of the droplets. Lesinurad nanosponges having a size range of 500 to 680 nm (nano meter) with normal frequency distribution was obtained.

In vitro dissolution studies of prepared Nanosponges:

Table No.4 Percentage of drug release of Nano-sponges (F1-F6)

Time	%CDR					
(hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	32.27±1.45	27.67±1.37	18.79±1.12	17.12±1.10	21.27±1.24	18.50±1.46
2	47.13±1.16	35.41±1.45	24.13±1.34	26.24±1.24	28.69±1.56	25.09±1.24
3	58.37±1.45	43.20±1.16	37.48±1.45	39.45±1.53	35.89±1.74	34.47±1.21
4	65.37±1.85	57.36±1.37	45.61±1.78	45.36±1.75	39.75±1.20	43.07±1.74
5	77.46±1.37	63.45±1.45	53.82±1.51	57.75±1.10	47.89±1.51	51.63±1.26
6	85.13±1.45	78.10±1.12	61.68±1.20	63.10±1.20	61.75±1.26	59.27±1.52
7	93.37±1.10	85.75±1.32	69.79±1.36	71.52±1.35	78.29±1.27	65.39±1.05
8	98.45±1.69	95.55±1.51	77.39±1.45	79.16±1.45	81.42±1.34	74.15±1.20
9		98.37±1.75	85.32±1.18	88.27±1.10	89.79±1.48	81.36±1.47
10			92.41±1.75	93.45±1.36	98.76±2.10	93.09±1.25
11			98.53±1.30	99.36±1.52		98.02±1.48
12						

Table No.5 Percentage of drug release of Nano-sponges (F7-F12)

Time	%CDR					
(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	17.34±1.24	10.48±1.54	35.42±1.24	34.38±1.65	17.09±1.21	15.34±125
2	34.75±1.56	18.64±1.69	48.15±1.73	41.79±1.24	25.47±1.49	23.75±1.27
3	41.12±1.57	25.27±1.57	56.05±1.62	49.63±2.15	37.07±1.26	29.12±1.65
4	49.28±1.46	34.69±1.45	63.72±1.57	55.78±1.58	42.63±1.47	37.28±1.20
5	56.18±1.21	39.89±1.20	71.34±1.95	62.69±1.74	49.27±1.52	43.18±1.78
6	67.34±1.74	46.75±1.38	79.65±1.54	69.12±1.52	58.39±1.62	51.34±1.51
7	75.25±1.52	53.89±1.45	86.67±1.51	78.79±1.62	63.15±1.27	60.25±1.20
8	81.84±1.20	68.75±1.32	93.67±1.28	86.42±1.20	75.36±1.67	67.84±1.65
9	87.63±1.85	82.29±1.45	98.95±1.54	93.24±1.57	86.09±1.45	75.63±1.37
10	92.65±1.64	89.42±1.65		98.45±1.65	92.02±1.26	86.65±1.45
11	98.48±1.57	92.79±1.57			98.42±1.38	93.12±1.20
12		98.16±1.45				99.15±1.37

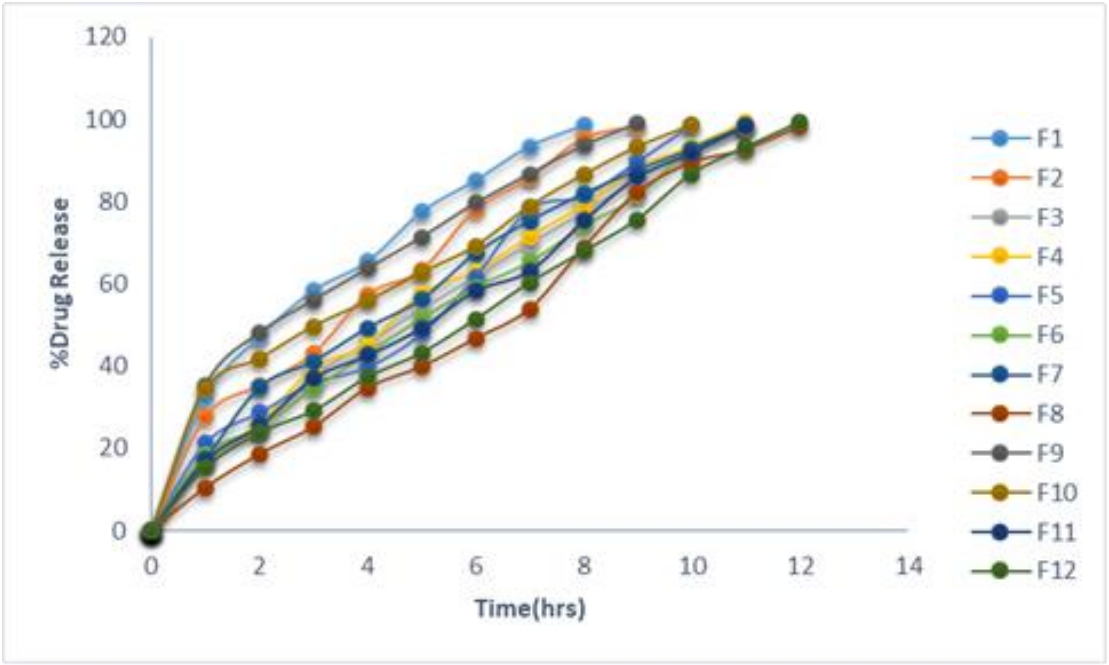

Figure.9 In vitro drug release of formulations F1-F12

Discussion:

By comparing the above dissolution studies of formulations F1-F12. Maximum drug release was found in F12 formulation containing Drug: Sodium Alginate in 1:2 ratio. So F12 formulation was taken as the optimized formulation, and drug release kinetics were performed for F12 formulation.

Kinetics Analysis for F12

Zero Order

Figure.10 Zero Order Plot for F12

First Order

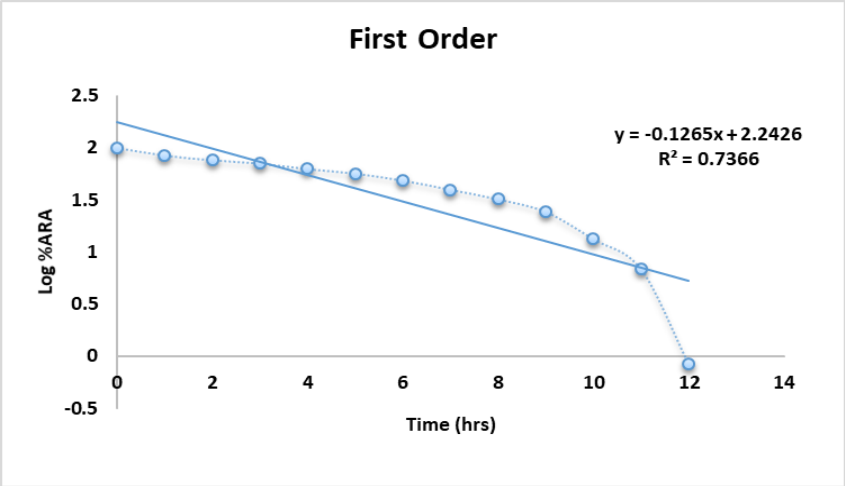

Figure.11 First Order Plot for F12

Higuchi Plot

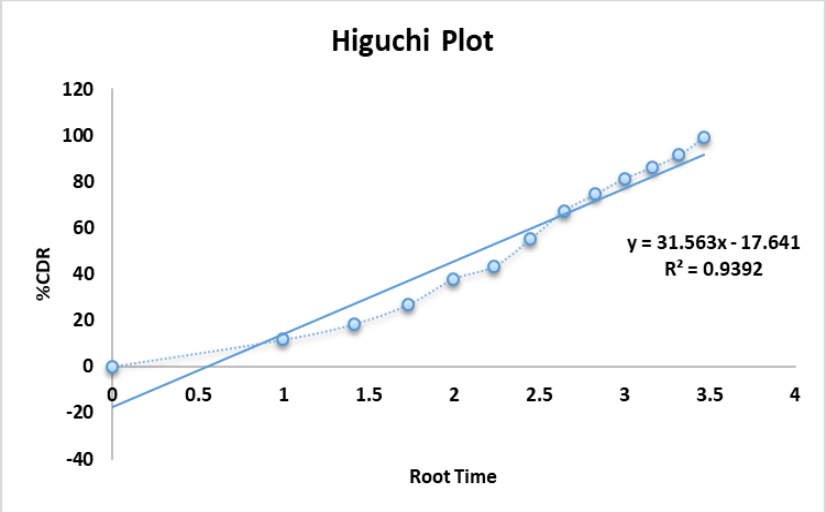

Figure.12 Higuchi Plot for F12

Peppas plot

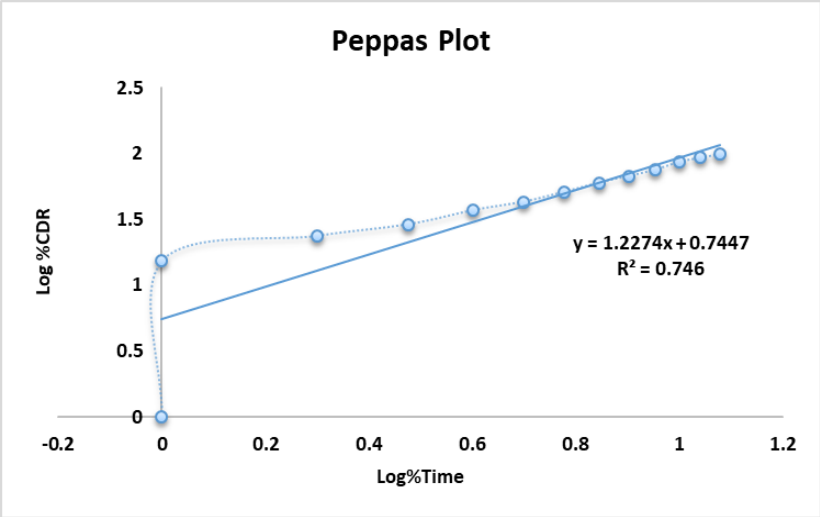

Figure.13 Peppas Plot for F12

Discussion:

The optimized formulation F12 has coefficient of determination (R2) values of 0.995, 0.736, 0.939 and 0.746 for Zero order, First order, Higuchi and Korsmeyer Peppas respectively. A good linearity was observed with the Zero order, 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 1.227 for optimized formulation. Thus n value indicates the Super case II transport. Thus, the release kinetics of the optimized formulation was best fitted into Zero order with Super case II transport.

SUMMARY AND CONCLUSION

The Lesinurad Nanosponge was prepared by solvent evaporation method using HPMC K4, Carbopol 934, Sodium Alginate as rate retarding polymers and PVA as co polymer using Dichloromethane 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 F12 has better results than other formulations. The F12 have its particle size 500nm, entrapment efficiency 99.16±1.15%, Among the polymers used such as HPMC K4, Carbopol 934, Sodium Alginate the drug polymers ratio of Lesinurad: Sodium Alginate (1:2) ratio sustains the drug release up to 12 hours. The F12 drug release was found to be 99.15±1.37% 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 these nano 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 (R2) values 0.995, 0.736, 0.939 and 0.746 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 1.227 for optimized formulation. Thus n value indicates the Super case II transport mechanism. Thus, the release kinetics of the optimized formulation was best fitted into Higuchi model and showed Zero order drug release with Super case II transport mechanism.

ACKNOWLEDGEMENT

The authors are thankful to the Department of Pharmaceutics, Malla Reddy College Of Pharmacy, Maisammaguda, Dhulapally (V), Affiliated to OU, Hyderabad, Telangana, India and Spectrum Pharma Research Solutions, Hyderabad, Telangana, India.

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