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Original Article

FORMULATION AND EVALUATION OF IBRUTINIB NANOSPONGES INCOPORATED TABLET

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ABSTRACT

Objective: The present investigation was undertaken to prepare polymeric nanosponges of an anti-cancer drug, ibrutinib to achieve controlled and improved drug release.

Methods: Nanosponges using a polymer (ethyl cellulose, poloxamer 188 and eudragit RL 30 D) and polyvinyl alcohol as a cross-linker were prepared successfully by the emulsion solvent evaporation method. Prepared nanosponges were evaluated for particle size, zeta potential, entrapment efficiency and *in vitro* drug release. Nanosponges with good drug release were formulated into tablets and evaluated for miromeritic properties, post-compression parameters and *in vitro* release and the final optimised formulation was characterized for globule size, zeta-potential, FTIR, SEM and stability studies.

Results: The nanosponges' particle sizes were discovered to range between 86.31 nm and 162.4 nm, the Zeta Potential ranges from-22.1 to-29. It was discovered that the drug entrapment efficiency ranged from 92.21 to 99.23% and Formulation F18 exhibited the highest drug release rate of 99.73% in 12h and was discovered to demonstrate good, satisfying results. The tablet formulation's micromeritic and post-compression parameters were examined, and it was discovered that F18 had good flow qualities. F18 had a mean globule size of 133.6 nm, a zeta potential of-22.1 mV, and SEM images revealed a sphere-like structure. The complexation of ibrutinib and the amorphous condition of the medication and formulation were confirmed by the FT-IR, and stability investigations to be stable for three months.

Conclusion: Hence, Ibrutinib loading into nanosponges made using the emulsion solvent evaporation process thus successfully boosted and controlled the drug release.

Keywords: Ibrutinib, Nanosponges, Anti-cancer agents, Poloxamer 188, Eudragit RL 30 D

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INTRODUCTION

Oral delivery of poorly water-soluble drugs in the form of nanosponge is a new and recent approach to overcome the aforementioned problems. Nanosponges contain microscopic particles of few nanometres-wide cavities in which a large variety of drug substances can be encapsulated. These microscopic particles are capable of carrying both hydrophilic and lipophilic substances and of enhancing the solubility of poorly water-soluble molecules [1]. Nanosponge shows a potential future in the coming years due to its variety of pharmaceutical applications like, extended-release, better product performance, elegance, improved physical, thermal and chemical stability, and reduced irritation [2]. Nanosponges are characterized by being highly stable and having the ability to carry both hydrophilic as well as hydrophobic drugs [3]. Different polymers can be used in formulating nanosponges, β-cyclodextrin is a commonly used polymer and it is cross-linked with a cross linker such as carbonyl or carboxylate to form the nanosponges [4]. Edragit RS 100 is also used in nanosponges formulation by the aid of ultrasonication, also solvent evaporation method can be used with ethyl cellulose (EC) to produce nanosponges [5].

Ibrutinib is a small molecule drug that inhibits B-cell proliferation and survival by irreversibly binding the protein Bruton's tyrosine kinase. Blocking BTK inhibits the B-cell receptor pathway, which is often aberrantly active in B-cell cancers. Ibrutinib displays an almost two-fold increase in its exposure when administered with food leads to decreased efficacy and safety of the drug. Due to poor solubility and hepatic first-pass effects, it is commercially available in capsular dosage form with very high doses (140 mg per capsule), which results in severe gastrointestinal adverse effects. Thus, an improved oral formulation of ibrutinib is required with better bioavailability and higher efficacy [6-9].

In the present investigation, an attempt was made to design and formulate nanosponges loaded tablet of the anticancer drug, ibrutinib, to prolonged drug release and with enhanced drug release.

MATERIALS AND METHODS

Materials

Ibrutinib was procured from Hetero Labs Ltd, Hyderabad. Ethylcellulose, Poloxamer 188, Eudragit RL 30D, Polyvinyl alcohol (PVA), Dichloromethane, Magnesum stearate, and Microcrystlline cellulose, were purchased from BASF, Mumbai, India. All the reagents used were of analytical grade.

Methods

Preparation of ibrutinib nanosponges

Emulsion solvent evaporation was used to make ibrutinib nanosponges. The nanosponges were made using three distinct polymers: ethyl cellulose, poloxamer 188 and eudragit RL 30 D Different amounts of polymers and polyvinyl alcohol (PVA) were used to make nanosponges. The disperse phase, which contained ibrutinib and polymer in 20 ml of dichloromethane, was slowly added to a specific amount of PVA in 100 ml of continuous aqueous phase using a magnetic stirrer at 1000rpm for 2 h. Filtration was used to collect the nanosponges, which were then dried in an oven at 40 °C for 24 h before being packed into vials. The following are the prepared ibrutinib nanosponges compositions with three distinct polymers listed in table 1 [10, 11].

Formulation of nanosponges tablet

Nanosponge tablets were prepared by direct compression method. The composition of the prepared nanosponge tablet formulations is shown in table 2. The prepared nanosponges and Excipients were accurately weighed and sieved. Tablet compression was carried out using 9 mm flat punches in a rotary tablet punching machine 8 [1].

Evaluation of nanosponges

Particle size, zeta potential and polydispersity index (PDI) measurement

The particle size of Ibrutinib nanosponges was measured by particle size analyser Horibo scientific nanopartical SZ100. For the

measurement 100 µl of the formulation was diluted with an appropriate volume of PBS pH 7.4 and vesicle diameter and zeta potential were determined. Each sample was measured three times, after which the average value was used for further calculations [12].

Table 1: Composition of ibrutinib nanosponges formulation (F1-F18)

Formulation code	Ibrutinib (mg)	Ethyl cellulose	Poloxamer 188	Eudragit RL 30 D	PVA (%w/v)	Dichloromethane (ml)	Water (ml)
F1	70	70			0.3	20	100
F2	70	140			0.3	20	100
F3	70	210			0.3	20	100
F4	70	280			0.3	20	100
F5	70	350			0.3	20	100
F6	70	420			0.3	20	100
F7	70		70		0.3	20	100
F8	70		140		0.3	20	100
F9	70		210		0.3	20	100
F10	70		280		0.3	20	100
F11	70		350		0.3	20	100
F12	70		420		0.3	20	100
F13	70			70	0.3	20	100
F14	70			140	0.3	20	100
F15	70			210	0.3	20	100
F16	70			280	0.3	20	100
F17	70			350	0.3	20	100
F18	70			420	0.3	20	100

Table 2: Composition of the nanosponges tablet formulation

Formulation code	Ibrutinib nanosponges (mg)	MCC (mg)	Magnesium stearate (mg)
F6	200	40	5
F12	200	40	5
F18	200	40	5

Entrapment efficiency

To calculate the entrapment efficiency, an accurately weighed quantity of nanosponges (10 mg) with 5 ml of methanolic HCl (HCl: Methanol-10:1) in a volumetric flask was shaken for 1 min using a vortex mixer. The volume was made upto 10 ml with Methanolic HCl. Then the solution was filtered and diluted and the concentration of Ibrutinib was determined spectrometric ally at 256 nm [13].

***In vitro* dissolution study**

Dissolution tests were performed with a USP Type I Dissolution Apparatus (basket type) in 900 ml of 3.0% w/v Polysorbate 20 in 50 mmol Phosphate Buffer, pH 6.8 at 37±0.5 °C and 100 rpm paddle rotation. The dissolving medium was encapsulated with a formulation containing 70 mg of ibrutinib (equal to a single dose). To maintain a consistent volume, 5 ml of material was taken and replaced with fresh dissolving medium (SGF) at specified time intervals. To determine the amount of medication released at each sampling point, the samples were spectrophotometrically examined at 259 nm [14].

Evaluation of nanosponge tablet formulations

Based on a good drug release profile and various evaluation parameters, three nanosponges formulations were out-listed and used for nanosponges tablet formulation. The nanosponge tablets formulation were first evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, carrs index and hausners ratio and Ibrutinib nanosponges tablet were prepared by direct compression method. The prepared nanosponge tablets were evaluated for their post-compression parameters like hardness, friability, drug content and *in vitro* drug release [15-17].

Pre-compression parameters

Bulk density: Bulk density of Nanosponges granules was determined by pouring gently 25 gm of the sample through a glass funnel into a 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as,

$$\text{Bulk density} = \text{Mass (gm)}/\text{Bulk Volume (ml)}$$

Tapped density: The tapped density was determined by pouring 25 gm sample (Nanosponges) through a glass funnel into a 100 ml graduated cylinder.

The cylinder was tapped from a height of 2 inches until a constant volume was obtained. The volume occupied by the sample after tapping was recorded and tapped density was calculated.

$$\text{Tapped density} = \text{Mass (gm)}/\text{Tapped Volume (ml)}$$

Carr's index (%): It is also one of the methods to evaluate flow property of a powder by comparing the bulk density and tapped density.

$$\text{CI (\%)} = [(\text{Tapped density} - \text{Bulk density})/\text{Tapped density}] \times 100$$

Hausner's ratio: It provides an indication of the degree of densification, which could result from the vibration of feed hopper.

$$\text{HR} = \text{Tapped density}/\text{Bulk density}$$

Angle of repose: Angle of repose was determined by fixed height method to characterize the flow property of granules. A funnel with 10 mm diameter of stem was fixed at the height of 2 cm over the platform. About 10 gm of the sample was slowly passed along the wall of the funnel till the tip of the pile formed touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose was calculated from the average radius using the following formula.

$$\text{Tan}\,\theta = h/r;\ \theta = \tan - 1h/r$$

Where θ = Angle of repose h = Height of the piler = Average radius of the powder cone

Post-compression parameters

Weight variation: It was determined as per IP 1996. Twenty tablets were selected randomly from each formulation, weighed individually, and the average weight and % variation of tablet weight was calculated.

Friability: The tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus.

After 100 revolutions, the tablets were dedusted and weighted again. The friability was determined as the percentage loss in weight of the tablets.

$$\% \text{ Friability} = (\text{Initial weight} - \text{Final weight}) * 100/\text{Initial weight}$$

Hardness: Hardness was measured using the Monsanto hardness tester.

Thickness: The thickness of the tablets was measured by using vernier calliper by picking the tablets randomly.

Drug content estimation

Ten Ibrutinib nanosponge tablets were accurately weighed, finely powdered and mixed. A portion of the powder equivalent to 20 mg of Ibrutinib was then transferred into a 100 ml volumetric flask and 60 ml of methanol was added. The contents of the flask were sonicated for 15 min and diluted to volume with methanol. 2 ml of this solution was then diluted to 100 ml volume with methanol. Absorbance of the resulting solution was measured at 259 nm using UV spectrophotometer. Drug concentration was determined from standard graph.

***In vitro* drug release studies of nanosponge tablet formulations**

In vitro drug release studies were carried out using USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm/min, 37±0.5 °C). Ibrutinib Nanosponge tablets were evaluated by exposing them to 900 ml 6.8pH phosphate buffer (simulated gastric fluid, SGF) for 12 h. The drug release at different time intervals was analyzed by UV double-beam spectrophotometer at 256 nm [14].

Characterization of the optimised formulation

Surface morphology

Scanning electron microscopy (JSM-5200, Tokyo Japan) was used to analyze particle size and surface topography was operated at 15kV acceleration voltage. A concentrated aqueous suspension was spread over a slab and dried under vacuum. The sample was shadowed in a cathodic evaporator with a gold layer 20 nm thick. Photographs were elaborated by an image processing program and individual NP diameters were measured to obtain mean particle size [18].

Accelerated stability studies

All formulations filled in hard gelatin capsules were packed in HDPE screw-capped bottles and kept in humidity chambers maintained at 40±2 °C/75±5% RH as per ICH guidelines for Zone III and stored for 3 mo [19].

RESULTS AND DISCUSSION

FTIR spectroscopy

The FTIR spectrum of Ibrutinib showed several characteristic peaks as shown in fig. 1 and it had characteristic peaks at 835.21, 943.22 and 1120 cm^{-1}, and the spectrum contained stretching vibrations of Ibrutinib C=O stretching vibration (1244.13 cm^{-1}), hydrocarbon stretching vibration of long fatty chain (2926.11 and 2858.60 cm^{-1}), and P–O stretching vibration (1112.96 cm^{-1}) one stretching vibration at 3396.76 cm^{-1} [20]. The presence of prominent characteristic peaks confirming the purity of ibrutinib as per the established standards.

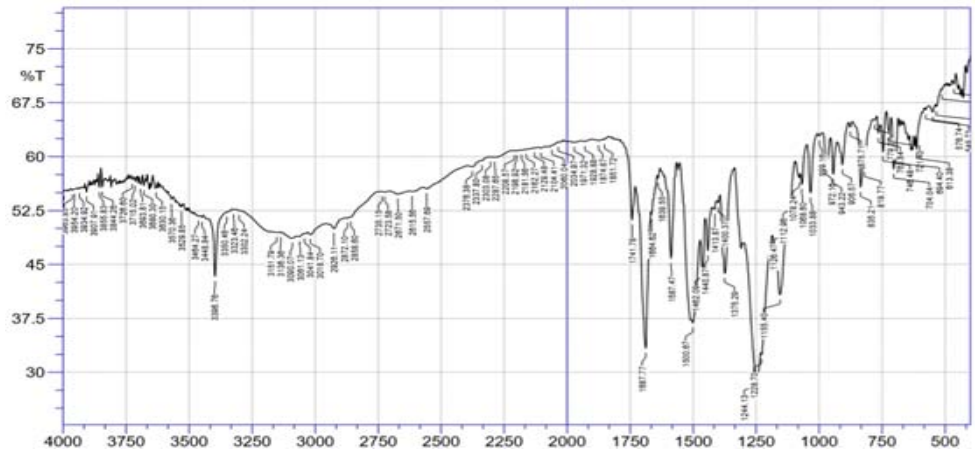


Fig. 1: FTIR spectrum of pure drug Ibrutinib

Mean particle size, zeta potential, polydispersity index and entrapment efficiency of ibrutinib nanosponges

A higher interfacial surface area for medication absorption is provided by a smaller droplet size. A smaller droplet size may also allow for a faster release rate. The particle size of the nanosponges was found to be between 86.31±4.64 and 162.4±1.16 nm, and the polydispersity index was found to be between 0.119±0.01 and 0.187±0.03.

The Zeta Potential was determined to be between 22.1±2.37 to-29.5±2.44.

The drug entrapment efficiency was found to be between 92.21±1.76 and 99.23±1.25. out of all formulation F18 was found to show good satisfactory results.

***In vitro* drug release of ibrutinib nanosponges**

The dissolving parameters of Ibrutinib pure drug and Ibrutinib nanosponges are compared fig. 2. The nanosponges form of ibrutinib was discovered to have a sustained release rate than the pure drug. In comparison to 31.25 percent in 60 min for pure drug, Ibrutinib nanosponges F1-F15 released more than 60% of the drug in 8 h. Formulation F18 exhibited the highest drug release rate of 99.73 percent in 12h. The nanosponges formulation's drug release increased proportionally with the polymer concentration, resulting in significant drug release in F18.

Micromeritic properties of nanosponges tablet formulation

Nanosponges formulation of ibrutinib with good drug release (F6, F12 and F18) were used to convert the nanosponges into tablet formulation. Micromeritic properties were studied for the tablet formulation and found F18 exhibited good flow properties compared to the other two (table 3).

Post compression parameters

The Post compression parameters of nanosponges tablet formulation (F6, F12 and F18) like average weight, hardness, thickness, friability and drug content, were studied and it found that F18 displayed best results out of three (table 4).

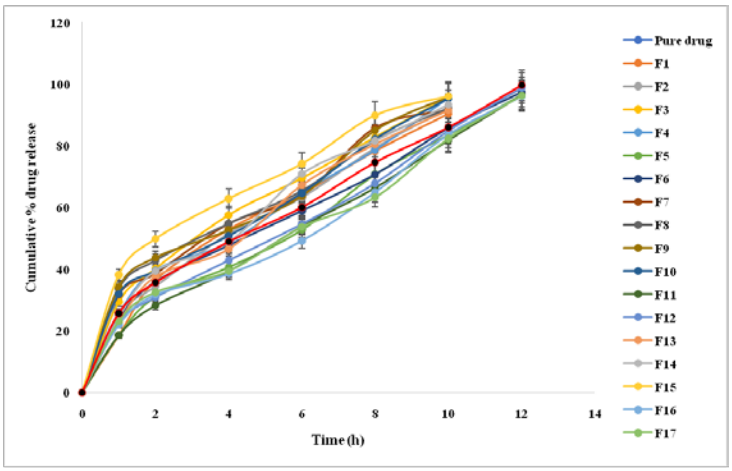


Fig. 2: Cumulative percentage drug release of Ibrutinib pure drug and Ibrutinib nanosponges (F1-F18), above parameters are communicated as maen±SD; (n=3)

Table 3: Micromeritic properties of nanosponges tablet formulation

Micrometric properties	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio	Angle of repose (°)
F6	0.45±0.87	0.48±0.78	14.74±0.53	1.17±0.78	27.46±0.45
F12	0.46±0.45	0.50±0.63	15.78±0.63	1.15±0.84	28.89±0.67
F18	0.48±0.86	0.52±0.64	13.54±0.34	1.16±0.60	27.31±0.23

Above parameters are communicated as mean±SD; (n=3)

Table 4: Average weight, hardness, thickness, friability and drug content of ibrutinib nanosponges tablet formulation (F6, F12 and F18)

Formulation code	Average weight (mg)	Thickness	Hardness	Friability	Drug content (%)
F6	244.07±1.46	4.75±0.23	7.61±0.74	0.21±0.07	97.45±0.14
F12	244.15±2.15	4.67±0.45	6.98±1.06	0.20±0.13	98.59±0.78
F18	245.2±1.68	4.34±0.96	6.8±0.31	0.19±0.32	99.89±0.67

Above parameters are communicated as mean±SD; (n=3)

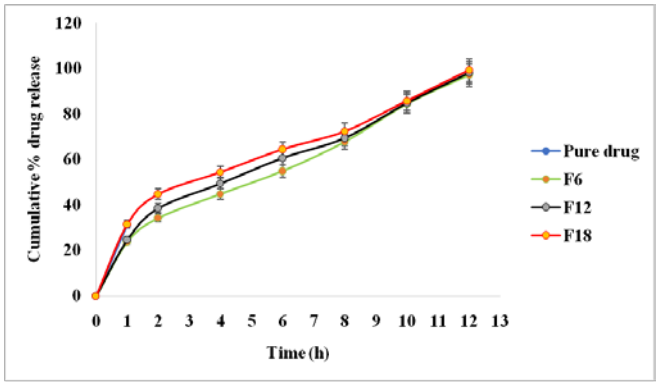


Fig. 3: *In vitro* drug release of ibrutinib pure drug and ibrutinib nanosponges tablet formulation (F6, F12 and F18), above parameters are communicated as mean±Standard Deviation; (n=3)

***In vitro* drug release of ibrutinib nanosponges tablet formulation**

The drug release of ibrutinib pure drug and ibrutinib nanosponges tablet formulation (F6, F12 and F18) was studied and found to be sustained for all formulations with the highest being for F18 formulation (fig. 3).

Characterization of final optimised formulation

Globule size and zeta potential

The globule size and zeta potential are the important parameters of the colloidal systems, which indicate the stability, static electricity repulsion and congregation of the globules [21]. Generally, an increase of electrostatic repulsive forces between nanoemulsion globules prevents the coalescence of nanoemulsion globules. Zeta potential is a measure for assessing these repulsive forces and was measured.

Globule size distribution and zeta potential of the optimised F18 formulation was analysed and fig. 4, 5 depict the optimized formulation's droplet size, and zeta potential, respectively.

The mean globule size of F18 was 133.6 nm indicating a nanoparticle range that facilitates absorption.

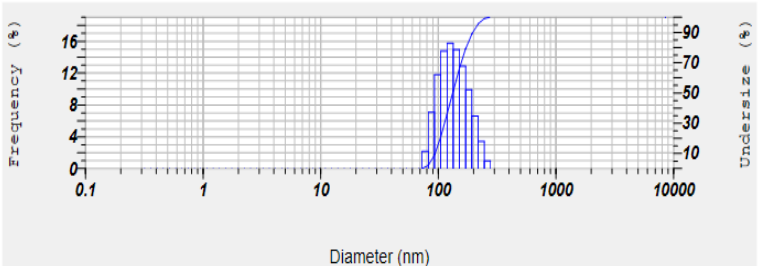


Fig. 4: Particle size of optimised nanosponges formulation of ibrutinib (F18 nanosponges)

Zeta potential of Ibrutinib nanosponges

The zeta potential (mean) values of nanosponges formulations were found to be in-22.1 mV. The zeta potential value>5 mV provide an excellent stability. For nanosponges higher zeta potential values infer stability and higher cellular uptake. In the present study, the zeta potential values of all the formulations is-22.1mV that is the constraint for particle stability (fig. 5).

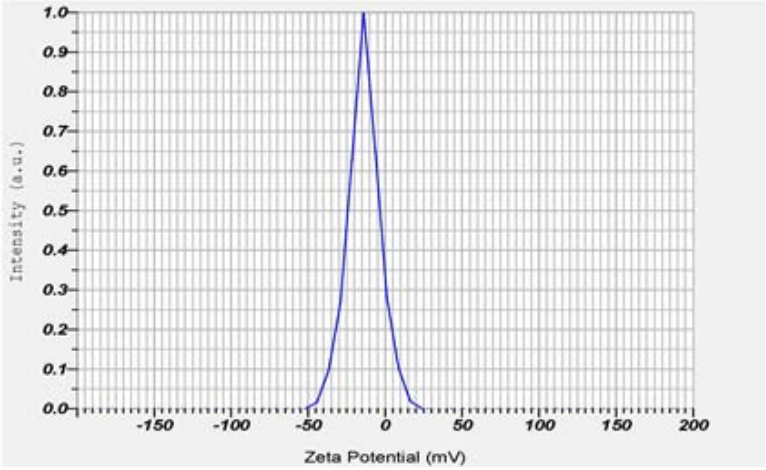
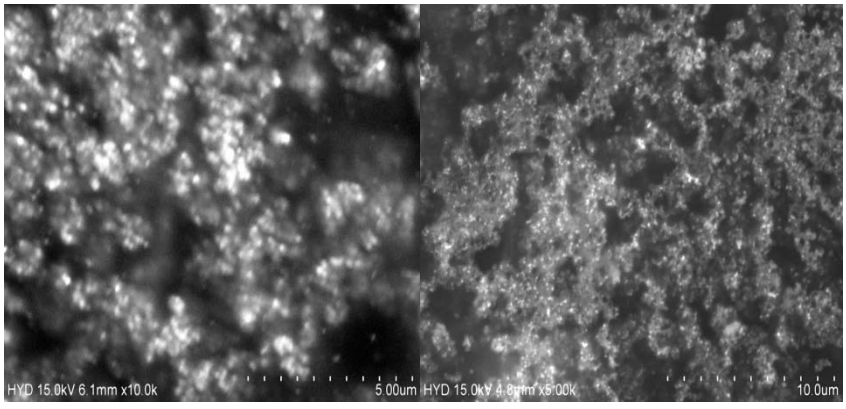


Fig. 5: Zeta potential of Ibrutinib nanosponges optimized formulation F18

Scanning electron microscopy (SEM) for Ibrutinib nanosponges

The morphology of nanosponges formulation was assessed using scanning electron microscopy. The optimised nanosponges (F18) formulation had a spherical shape with a uniform and somewhat narrow particle distribution, according to the results [22, 23]. The droplets seemed distinct, with no evidence of drug precipitation, implying that the formulation was stable (fig. 6 A and 6B).



(6A) **(6B)**

Fig. 6A and 6B: scanning electron microscopy images of Ibrutinib optimized nanosponge tablet formulation (F18)

Stability studies

No visible physical changes were observed in all the formulations withdrawn from the humidity chambers. The samples were assayed for % drug content and *in vitro* drug release and the results are shown in table 5. No significant difference was observed after storage at accelerated conditions at 40±2 °C/75±5% RH for a period of 3 mo.

Table 5: Storage at 40±2 °C/75±5% RH for 3 mo

Retest time for optimized formulation F18	% Drug content	*In vitro* drug release (%)
0 d	99.89±0.67	99.21±1.83
30 d	98.21±0.45	99.02±1.56
60 d	97.70±0.78	98.65±0.23
90 d	97.09±0.36	98.12±0.69

Above parameters are communicated as mean±SD; (n=3)

CONCLUSION

Nanosponges are one of the recently advanced drug delivery systems with sponge-like structures that entrap drug molecules to form an inclusion complex. This study successfully designed nanosponges using polymer and crosslinker by emulsion solvent evaporation technique. The particle sizes of ibrutinib nanosponges ranged within 86.31 nm and 162.4 nm. Zeta potential was optimally higher to get a stable colloidal nanosuspension. The prepared nanosponges with good drug release (F18=99.73% in 12h) were formulated into tablets and F18 displayed satisfactory micromeritic and post-compression parameters. Drug interaction with nanosponges was established by FTIR and SEM studies and stability studies to be stable for three months. A slow sustained drug release was observed for drug-loaded nanosponges with comparatively higher drug release relative to pure drug.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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