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Original Research Article

Comparison of solvent evaporation and ultrasonic-assisted production methods in the development of nimesulide nanosponges and their characterization

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Abstract

Purpose: *To compare solvent evaporation and ultrasonic assisted synthesis in preparation of nimesulide nanosponges using polyvinyl-alcohol and Eudragit L100 as a polymer/copolymer and dichloromethane as a cross linker.*
Methods: *Twelve formulations of nimesulide were prepared, six with each method by varying the ratios of both polymer and co-polymer. The resulting nanosponges were evaluated characterized by pre-formulation studies, production yield (%), differential scanning calorimeter, x-ray diffraction, Fourier transformation infrared spectroscopy, scanning electron microscopy, entrapment efficiency (%), actual drug content (%) and in-vitro dissolution studies.*
Results: *The results revealed that the formulation with high amounts of co-polymer in both methods showed crystalline structures with enhanced dissolution rates in basic media. Drug entrapment was higher for products prepared by solvent evaporation method (74 %) than that prepared by ultrasonic assisted method (61 %). This correlates with the enhanced dissolution rates for products by solvent evaporation method and increased solubility due to drug-polymer complex formation.*
Conclusion: *Formulations made by solvent evaporation method demonstrate higher production yield and drug entrapment. However, both methods exhibit enhanced dissolution rates in basic medium generally as well as other characteristics that are comparable to nanosponges reported in the literature with regard to their comb like structure.*

Keywords: *Nanosponges, Nimesulide, Emulsion solvent diffusion, Ultrasonic-assisted synthesis, Sustained release*

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INTRODUCTION

International association for the study of pain (IASP) defines pain as a disturbed sensory experience related to emotions which is associated with central and peripheral nervous system [1]. Nimesulide is a NSAID which is weakly acidic with a pKa of 6.5 and contains sulfonamide moiety [2]. Nimesulide is a COX II inhibitor and has good anti-inflammatory, analgesic and antipyretic activity with non-significant gastro duodenal side effects [3].

Nimesulide belongs to Class II of BCS classification which means that the rate limiting step for the drug absorption is the dissolution rate of the drug. According to the biopharmaceutical classification system (BCS) Class II drugs are characterized by their High permeation and Low solubility in human body [4]. The major issues faced by the researchers in development of the drug are the sustain release technology which is used to reduce the GIT irritation of the drug. All drugs of BCS Class II are potent candidates for formulation of nanosponges. As the BCS class II drugs are drugs which require solubility to be improved but no study has been carried out of formation of nanosponges of nimesulide to study the efficacy of targeted drug delivery [5]. Micro- and nano-structures in dosage forms are deployed to provide better results to patients and overcome the solubility and GIT issues [6].

Nanosponges are network or scaffold which are made up of polymers and other materials used for targeted drug delivery. They have small sizes of less than 1 µm and occur in crystalline and para-crystalline forms. The tiny sponges have the ability to entrap poorly soluble drugs and in return enhance the solubility of the drug and also release the drug at targeted site in controlled manner [8]. The common characteristics of types of nanosponges are the presence of nano scale pores that give them particular properties [9,10].

Solvent (Emulsion) diffusion method, quasi-emulsion solvent diffusion, solvent evaporation method, and ultrasound-assisted synthesis are the methods described in different literatures to produce nanosponges [11]. This research aimed to develop nanosponge formulations of nimesulide using solvent evaporation and ultrasound assisted synthesis as both methods are easy to apply, require minimum equipment and which can enhance the solubility of the drug but also prolong the release of the drug from the nanosponges structure using Eudragit L100 [7], PVA and Dichloromethane [12-14].

EXPERIMENTAL

Materials

Nimesulide was a gift from Pharm-Evo Pharma (Pvt) Ltd, Karachi, Pakistan. Eudragit L100, (EL100), polyvinyl alcohol (PVA), and dichloromethane (DCM) were gift samples from Jawa Pharmaceuticals, Lahore, Pakistan. All other chemicals used were of analytical grade.

Formulation of nimesulide nanosponges

Nimesulide, Eudragit L100, polyvinyl alcohol and dichloromethane were used to prepare the formulation using two different methods, solvent evaporation method and ultrasound assisted synthesis. A Total of 12 formulations, were prepared by varying the drug to polymer ratios, while also varying the ratio of copolymer with each drug/polymer ratio while keeping cross-linker (dichloromethance) quantity as constant i.e., 20ml for each formulation. Formulations N1 - N6 were prepared using solvent evaporation method [15], while formulations N7 – N12 were prepared using ultrasonic assisted synthesis method. The composition of the formulations are presented in Table 1.

Table 1: Composition of nimesulide nanosponges

Formulation	Method used	Drug Content (g)	Polymer Eudragit L100 (g)	Drug: polymer ratio	Co-polymer (PVA) (%w/v)
N1	Solvent evaporation method	2	1	2:1	0.5
N2		2	2	1:1	0.5
N3		2	3	1:1.5	0.5
N4		2	1	2:1	0.75
N5		2	2	1:1	0.75
N6		2	3	1:1.5	0.75
N7	Ultrasonic assisted synthesis	2	1	2:1	0.5
N8		2	2	1:1	0.5
N9		2	3	1:1.5	0.5
N10		2	1	2:1	0.75
N11		2	2	1:1	0.75
N12		2	3	1:1.5	0.75

Solvent evaporation method

Two phases were prepared i.e., dispersion phase and the aqueous phase. Dispersion phase consisted of polymer (Eudragit L100) and drug dissolved in dichloromethane while the aqueous phase was prepared by dissolving PVA in 150 mL water for 30 min while stirring. Afterwards, the aqueous phase was added drop wise to the dispersion phase while stirring continuously at 1000 rpm for 2 h. The product obtained was filtered and dried at 40 ºC for 24 h. The dried samples were store in airtight container for characterization.

Ultrasonic-assisted method

Eudragit L100, drug, PVA and dichloromethane were mixed together, and sonicated at 37KHz at 80 ºC for at least 5 h using elmasonic S(30) H till complete evaporation of the solvent. The samples were cooled, washed with water and dried using Soxhlet extraction with ethanol. The dried samples were stored in airtight container for characterization.

Production yield (PY)

The production yield of formulations was calculated as shown in Eq 1, based on the initial and final weights of the formulation in grams, using an analytical balance with a maximum capacity of 210 g and readability of 0.0001 g.

$$Yield\ (\%) = \frac{WNS}{WRM} \times \frac{100}{1} \quad \ldots\ldots\ldots\ldots (1)$$

where WNS= weight of nanosponge obtained and WRM= weight of raw materials (polymer + drug).

Assessment of pre-formulation parameters

Compressibility index (Carr's index)

Carr's index (C) is an indirect measurement of bulk density, size and shape, surface area, moisture content, and cohesiveness of material. Carr index (%) is determined by Eq 2.

$$C\ (\%) = (Bd - Td)/Td\}100 \quad \ldots\ldots\ldots\ldots (2)$$

where Bd and TD are bulk and tap densities, respectively.

Entrapment efficiency (EE)

The entrapment efficiency and actual drug content of the formulations were determined by weighing an amount of each formulation theoretically equivalent to 100 mg of nimesulide. It was transferred to a 100 mL volumetric flask and 0.1 M NaOH was added. Nimesulide content was determined spectrophotometrically using UV-Visible spectrophotometer UV-1800 SHIMADZU-JAPAN at wavelength of 392 nm. EE was calculated using Eq 2.

$$EE\ (\%) = \frac{A}{T} \times 100 \quad \ldots\ldots\ldots (2)$$

where A= drug content (actual) and T = drug content (theoretical).

Scanning electron microscopy (SEM)

Microscopy studies were carried out using an Optika microscope with 20x magnification lens and the images were recorded, while SEM microscopy was carried out for four formulations with the lowest and highest polymer concentrations (N1 and N6 for solvent evaporation method, N7 and N12 for ultrasonic assisted synthesis method). The images were drawn at less than 100 µm level [16].

Fourier transform infrared (FTIR) spectroscopy

The FTIR analysis of all twelve formulations was carried out on FTIR-Shimadzu (model no. IRPRESTIGE21, Japan). For measurement of sample ATR (attenuated total reflectance) was used where sample was clamped firmly to the prism and large contact surface area was ensured to get the good sensitivity in results. Spectrum is taken through the depth of few µm within the sample The data was subjected to multipoint calibration function in IR solutions software of FTIR and resulting calibration curve was obtained. For the multi-point calibration the concentrations of amount of drug available in formulation was put into the system and results were obtained on a curve for all the formulations [17].

Differential scanning calorimetry

Differential scanning calorimetry was carried out on two formulations N6 and N12 using sample size of almost 24 mg with the aid of nitrogen gas at flow rate of 100.0 ml/min and the controls were set to 0.5 s/pt. Data was obtained for both the heat flow and percentage weight loss as a function of time. The shift of the melting point as reported in the literature of the pure drug gives evidence that the drug is well incorporated into the nanosponges and nanosponges can be processed at higher temperature and can impart more stability to the formulation.

In vitro drug release studies

In vitro release of nimesulide from the nanosponges was determined in 3 different mediums i.e., 0.1 M HCl (pH 1.2), water (pH 6.5) and phosphate buffer (pH 6.8) separately. The amount of nanosponges equivalent to 100 mg of nimesulide was transferred into 900 mL of dissolution medium at 37ºC in a USP apparatus operated at 100 rpm. Samples are drawn at intervals of 30, 60 and 120 min and are analyzed spectrophotometrically at 392 nm.

RESULTS

Production yield

The results are shown in Table 2. All production yields range from 51.80% (solvent evaporation) to 91.09% (ultrasonic assisted synthesis).

Flow rate

The results of flow property is presented in Table 3. Flow properties of all the formulations of pure nimesulide were modified from hygroscopic and not free flowing powder form to a free-flowing form. Increase in the concentration of the polymers reduced the flow properties of the complex. In case of higher concentrations of polymer in N6 and N12 in both methods the Carr's index was in the passable and fair range.

Fourier transform infra-red spectra

The FTIR spectra of the pure drug and all formulations were obtained in the 4000 to 400 cm^{-1} range. The spectrum of the pure drug shows characteristic peaks pertaining to C-H aromatic ring from 906 - 640 cm^{-1}. It showed S=O at 1078cm-1, 1159cm-1 for C-O-C ether linkage, 1077cm^{-1} for CH3 CH bending. Also at 1516 & 1340 cm-1 for NO_2 and 3286 cm^{-1} for presence of Alkynes C-H stretch and O-H stretching. Peaks between 1589 to 1153 correspond to NO_2 asymmetrical stretch and -CN amine stretch. All formulations showed the same characteristic pattern of peaks which indicates that there was no chemical interaction between the polymer and the drug. In combined spectra overlapping pattern at a single point on the calibration curve within the area point shows no shifts in peaks and no chemical interaction [19].

Table 2: Production yield of nimesulide in nanosponge formulations

Formulation	Initial weight of materials (WNS) (g)	Final weight of formulation (WRS) (g)	Production yield (%)
N1	3.5	2.4658	70.45
N2	4.5	3.4657	77.01
N3	5.5	5.0100	91.09
N4	3.75	2.8698	76.52
N5	4.75	4.2670	89.83
N6	5.75	4.9175	85.52
N7	5	4.2607	85.21
N8	4.5	2.3310	51.80
N9	5.5	4.1270	75.03
N10	3.75	1.9065	50.84
N11	4.75	3.4611	72.86
N12	5.75	4.1814	72.72

Table 3: Hausner's Ratio**,** entrapment efficiency and actual drug content

Formulation	Hausner's Ratio	Flow Character	EE (%)	Actual drug content (%)
N1	1.11	Excellent	68.32	68.02
N2	1.04	Good	51.22	51.00
N3	1.25	Fair	52.41	52.18
N4	1.17	Fair	74.10	73.78
N5	1.23	Fair	50.32	50.10
N6	1.27	Passable	74.58	74.26
N7	1.05	Excellent	61.89	61.62
N8	1.20	Fair	49.34	49.13
N9	1.19	Fair	68.15	67.86
N10	1.31	Passable	51.76	51.54
N11	1.30	Passable	59.96	59.70
N12	1.25	Fair	61.41	61.14

Drug content and entrapment efficiency

The results of entrapment efficiency or actual drug content are presented in Table 3. The percentage ADC results show that as the polymer concentration increases, the volume of the complex formation between the drug and the polymer also increase and more will be the drug concentration in the specified medium.

Morphology of the formulations

The results of SEM are presented in Figure 2. The SEM microscopy images were obtained at less than 100 µm level at magnification of X5,000

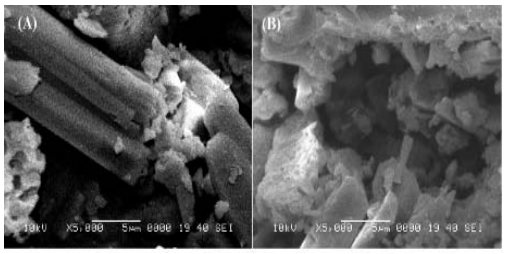

Figure 2: (a) SEM micrograph of formulation N6; (b) SEM micrograph of formulation N12

Thermal characteristics of the formulations

The DSC thermograms are presented in Figure 3.

In vitro drug release

The *in vitro* drug release study results are presented in Table 4. The release data of nanosponges shows that increase in the concentration of the drug and the polymer/copolymer ratio decreases the rate of release from the nanosponges. The release rate is maximum with the minimum polymer ratio, i.e., N1, N3 and N6. Nimesulide is released from nanosponges in basic medium. The release of the active drug from the nanosponges is a complex process which is affected by many factors such as binding affinity between polymer and drug, polymer degradation speed, and pH.

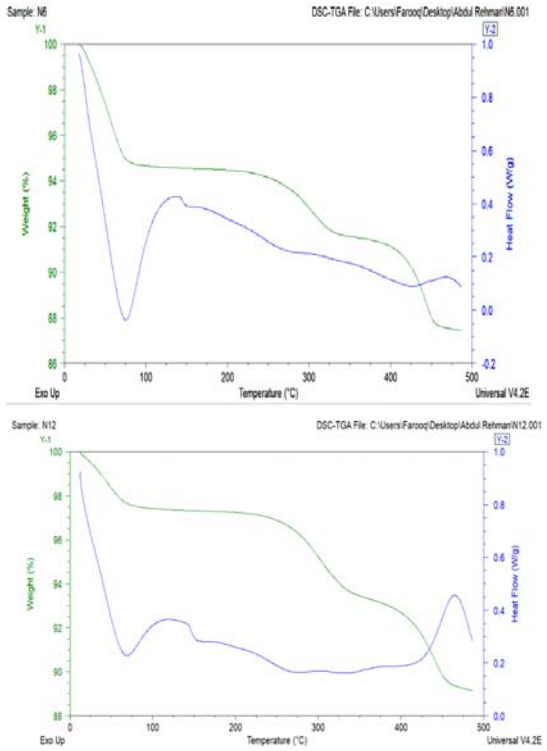

Figure 3: (a) DSC thermogram of (a) formulation N6 and (b) formulation N12

Table 4: *In vitro* drug release profile of nimesulide from formulation N1 – N12 in (a) 0.1 M HCl medium; (b) distilled water (c) phosphate buffer (pH 6.8 medium)

Formulation	0.1M HCl (30min)	0.1M HCl (60min)	0.1M HCl (120min)	Water (PH 6.5, 30 min)	Water (PH 6.5, 60 min)	Phosphate buffer (pH 6.8, 30 min)	Phosphate buffer (pH 6.8, 60 min)	Phosphate buffer (pH 6.8, 120 min)
N1	4.95%	7.19%	11.98%	7.67%	35.47%	24.6%	40.42%	49.69%
N2	4.95%	5.59%	7.51%	6.87%	9.95%	30.51%	39.78%	44.42%
N3	8.46%	8.94%	25.72%	10.86%	21.89%	50.8%	52.08%	70.14%
N4	4.79%	4.79%	17.73%	8.94%	22.53%	31.47%	38.5%	54.49%
N5	15.50%	17.25%	19.65%	10.06%	16.46%	48.26%	58.79%	61.04%
N6	11.34%	14.38%	36.27%	16.77%	31.48%	50.97%	57.68%	84.85%
N7	2.39%	7.67%	8.94%	10.06%	14.22%	42.98%	48.9%	53.86%
N8	2.39%	6.23%	9.90%	5.91%	6.87%	20.92%	32.43%	53.36%
N9	4.15%	4.79%	11.82%	5.43%	9.90%	13.57%	29.71%	37.06%
N10	2.077%	2.55%	7.51%	5.29%	29.40%	11.98%	19.16%	25.56%
N11	6.87%	10.86%	13.42%	4.31%	7.35%	19.81%	31.31%	35.15%
N12	4.95%	6.71%	13.90%	2.07%	6.87%	22.68%	29.24%	37.39%

DISCUSSION

Twelve nimesulide nanosponges formulations were prepared by ultrasonic and solvent evaporation methods. Eudragit L100 and PVA were used as copolymer/polymer with DCM as the crosslinker.

All nanosponge formulations were formed with porous cavities and drug entrapment, presented the crystalline nature. Nimulsuide was physically attached with the polymer in the form of a complex network that enhanced the dissolution rate and preformulation properties of the drug. The nanosponge formulations were a non-swellable complex, based on the drug release data, and followed the matrix diffusion release mechanism. Nanosponge formulations prepared from ultrasonic method presented both diffusion and erosion drug release mechanisms.

FTIR analysis showed that there was no chemical interaction between the polymers and drug. All the drug distinct peaks were intact. The two formulations that were selected, optimized and characterized by SEM and DSC suggest that there was recrystallization of the nanosponge formulations. An endothermic peak at 75 – 80 ºC was observed in both formulations. In case of N6 formulation, the shift in melting was due to presence of liquid for vaporization. A slight dip at temperature of almost 140 – 150 ºC probably indicate miscibility of the pure drug with the polymer, and the complex formation between the drug and the polymer.

CONCLUSION

Nanosponges have successfully generated by both solvent evaporation and ultrasonic-assisted synthesis. The nanosponges prepared from ultrasonic assisted method demonstrate higher dissolution rates in basic media than those obtained by solvent evaporation, and possess the comb-like structure of nanosponges reported in the literature. The generated nanosponges are potentially suitable for the production of other dosage forms, including tablets, capsules and even injectables form.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Pervaiz Akhtar Shah: Manuscript writing, Conduct the study,Haroon Khalid Syed: Data Analysis, resources,Abdul Rehman Sohail: Methodology, Data analysis, Areeba Pervaiz: Data analysis, Muhammad Shahid Iqbal: Data Analysis, resources, Kai Bin Liew: Revising and editing the manuscript

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