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FORMULATION AND *IN-VITRO* EVALUATION OF GLIPIZIDE LOADED NANOSPONGES

Pharmacy

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ABSTRACT

The present research work is aimed to formulate Glipizide loaded nanosponges using simple and cost effective method. Nanosponges were prepared by "Emulsion solvent evaporation method" using different polymers like ethyl cellulose and polyvinyl alcohol, and a cross-linking agent like dichloromethane. Further, they were evaluated for entrapment efficiency and *in-vitro* dissolution studies. The selected N7 batch was further subjected to surface morphological investigations, using FE-SEM, where results showed that the nanosponges are of spherical uniform shape with a spongy structure. The entrapment efficiency of N7 batch was found to be 87.2% and the drug release of the formulation (N7) was found to be 70.8% after 10hrs. Particle size of the batch (N7) of nanosponges was observed as 441nm. Zeta potential was found to be -18.63mV and SEM revealed the rough and porous surface of the prepared nanosponges.

KEYWORDS

Glipizide, Ethyl Cellulose, Polyvinyl Alcohol, Dichloromethane, Nanosponges delivery system (NDS).

INTRODUCTION

Oral hypoglycemic agents such as sulfonylureas are a treatment option for patients with type 2 diabetes, especially those with diseases under the age of 40 years (1). This class of drugs works by binding the sulfonylurea receptor to pancreatic beta cells thereby enhancing insulin secretion from the pancreas by inhibiting the production of hepatic glucose when transported through the portal artery. Sulfonylureas agents have many problems such as low melting, general management and early metabolism (2). Glipizide is a fast-acting anti-diabetic drug that works in the sulfonylurea class. It comes under the category of second-generation sulfonylurea, with a short half-life of 2-4 hours (3, 4).

There has therefore been a lot of emphasis placed on the development of new drug delivery systems to provide the medical agent with the required amount, at the right time, in the right place in the body, in a way that works well, increases compliance and reduces side effects (5). Solid drug delivery uses devices such as nanosponges, nanoparticles, nanocapsules, or nanotubes that incorporate drugs and release them at controlled doses for an extended period of time (6). While various devices have been used for continuous drug delivery, nanosponges represent a novel class of encapsulating nanoparticles that have made an appearance as a promising delivery system in both the cosmoceuticals and pharmaceuticals field (7). Nanosponges are virus-sized, sponge-like nanoparticles with an average diameter below 1 µm that possess a porous surface and a non-collapsible structure (8). Nanosponges are one of the most common and hold several benefits. The attraction of formulating Nanosponge drug delivery system lies in their ability to incorporate hydrophobic drugs, thereby enhancing their solubility (9). Because of their nanoporous structure, nanosponges can carry water insoluble drugs especially for BCS class-II drugs. These complexes are used to increase the dissolution rate, solubility and stability of drugs (10). After reaches in the site of action, Nanosponge adhere on the surface of organ and then release the drug for extended period of time in a controlled manner. Nanosponges are non-irritating, non-mutagenic, non-allergenic and non-toxic, which reduces side effects and improved stability (11).

Ethyl cellulose is a cellulose derivative and hydrophobic, non-swellable polymer that is practically insoluble in water but soluble in various organic solvents, including methylene chloride and alcohol. It has been comprehensively used in micro-encapsulation (12, 13).

By creating Glipizide-loaded Nanosponges using ethyl cellulose as a polymer, the drug release will be strengthened so that the duration of the duration will be reduced and eliminate the absorption variance (14).

MATERIALS AND METHODS

Materials

Glipizide was purchased from Horizon Bioceuticals Pvt. Ltd., Ethyl cellulose was purchased from Loba Chemie Laboratories Mumbai, Poly vinyl alcohol, Dichloromethane and Methanol were obtained from Nice Laboratories Reagents, Kochi.

Design and preparation of Glipizide loaded Nanosponges Emulsion solvent evaporation technique was used to prepare Glipizide loaded Nanosponges (15). To prepare the organic phase Ethyl Cellulose was weighed accurately and dissolved in dichloromethane. Glipizide (10 mg) was added to the organic phase. Then the organic phase was poured into aqueous phase containing PVA solution. The mixture was stirred at 600-1200 rpm for 1-3 hrs. The prepared Nanosponges were then filtered by vacuum filtration and dried at room temperature and then stored in vacuum dessicator for further evaluation.

Table 1: Formulations of Nanosponges

Batch Code	Standard Order	A(mg)	B (rpm)	C (hrs)
F1	1	150:150	600	1
F2	2	150:450	600	1
F3	3	150:150	1200	1
F4	4	150:450	1200	1
F5	5	150:150	600	3
F6	6	150:450	600	3
F7	7	150:150	1200	3
F8	8	150:450	1200	3

A, Ethyl cellulose: Poly vinyl alcohol ratio; B, Stirring speed; C, Stirring time.

Evaluation Of Optimized Batch Of Nanosponges

Particle size analysis

The particle sizes of the prepared Nanosponges were measured by Beckman Coulter Delsa™ Nano C Particle Analyzer. The dried powder samples were suspended in deionised water and sonicated for one minute with an ultra-sound probe before measurement.

Surface and shape analysis by Scanning Electron Microscopy

The surface characteristics and shape of nanosponges were analysed by FE SEM operating at 10 kv. The samples were mounted on an aluminium stub with adhesive tape and excess samples were removed and coated with gold for 20 seconds. Then the metal stub was placed in E-1010 Ion sputter for 20 minutes under vacuum. After 20 minutes, samples were analyzed under FE-SEM.

Entrapment Efficiency

The EE of the NGs was determined spectrophotometrically. A sample of glipizide nanosponges (10 mg) was dissolved in 10 ml of methanol and kept it for overnight. 1 ml of the supernatant was taken and diluted to 10 ml with a solution containing phosphate buffer of pH 7.4 and was analysed at 223 nm using UV-Visible spectrophotometer (16). From the absorbance, % EE of the nanosponges was calculated by the following Equation:

$$\% \text{ Entrapment Efficiency} = \frac{\text{actual drug content}}{\text{practical drug content}} \times 100$$

Eq. 1

Zeta Potential

Zeta potential is a measure of surface charge of dispersed particles in relation to dispersion medium. The charge of the nanosponge was determined by Beckman Coulter Delsa™ Nano C Particle Analyzer. The experiment was conducted using clear disposable zeta cell, water as dispersant which has refractive index (RI) -1.330 and viscosity (cPs) -0.88 and the temperature was kept constant at 25°C. In order to minimize the error, the sample was analysed three times.

***In-vitro* drug release study**

Apparatus - USP-II dissolution apparatus (Paddle)
Medium - Phosphate buffer of pH 7.4
Temperature - 37°C
Time - 10 hours.

Procedure: *In vitro* release study was performed using USP Paddle method at 100 rpm and 37 ± 0.2°C in 900 ml of phosphate buffer pH 7.4 (17). 100 mg of the formulated nanosponges were used for the experiment. Five ml aliquots were withdrawn at 30, 60 and 120th min and the hourly intervals upto 12 hours and a last aliquot was withdrawn at 16th and 24th hour. The samples after filtration were analyzed at 223 nm. Fresh dissolution medium was replenished each time when sample was withdrawn to compensate the volume.

RESULT AND DISCUSSION

Particle Size Analysis by Beckman Coulter

Particle size analysis is performed by Beckman Coulter and average size of particles is reported as 441.8 nm as shown in Figure 1.

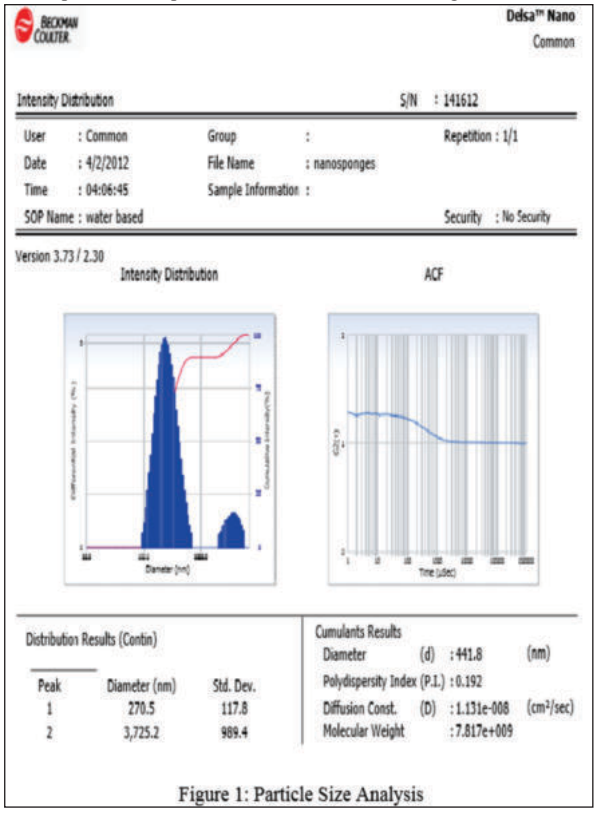

Figure 1: Particle Size Analysis

Surface analysis and shape by Scanning Electron Microscopy

Surface morphology of the Nanosponges was examined by FE SEM as shown in figure 2 and figure 3. SEM analysis revealed nanosized, almost spherical particles with numerous pores on the surface. The pores characteristically tunnelled inwards that were probably the impressions of diffusion of solvent (dichloromethane) from the surface of Nanosponges. Any residual crystals of the drug could not be seen on the surface of the Nanosponges indicative of the matrix being construtcted from drug and polymer.

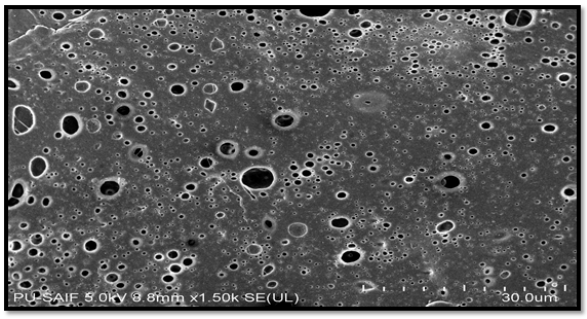

Figure 2: SEM photograph of Glipizide loaded Nanosponges

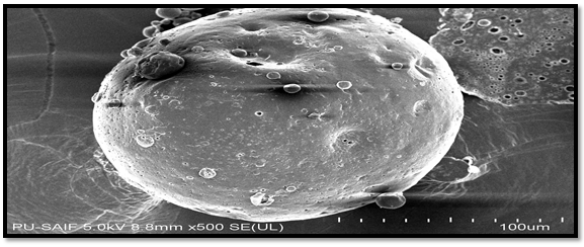

Figure 3: SEM photograph of Glipizide loaded Nanosponges

Zeta Potential

Zeta potential was performed by Beckman Coulter, Zetasizer and the average zeta potential was reported as -18.63 (mV) as shown in Figure 4.

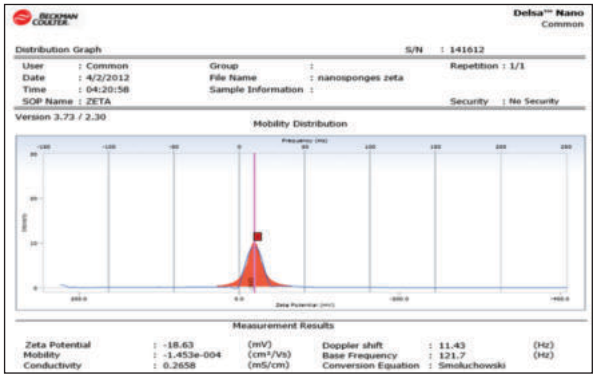

Figure 4: Zeta Potential Analysis

Entrapment Efficiency

Entrapment Efficiency of eight batches (N1-N8) is summarized in Table 2.

Table 2: Entrapment Efficiency of Nanosponges

Batch Code	Entrapment Efficiency (%)
N1	70.3 ± 0.69
N2	65.4 ± 0.45
N3	79.5 ± 1.12
N4	68.8 ± 1.90
N5	74.1 ± 1.73
N6	75.7 ± 0.69
N7	87.2 ± 1.14
N8	84.9 ± 0.78

Drug Dissolution Study

Drug dissolution of eight batches (N1-N8) is summarized in Table 3 and in Figure 5.

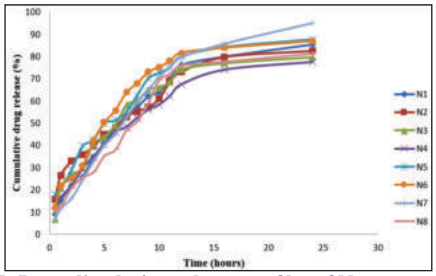

Figure 5: Drug dissolution release profiles of Nanosponges

Table 3: Drug Dissolution Data of Nanosponges

Time (hrs)	N1	N2	N3	N4	N5	N6	N7	N8
0.5	85.23± 0.50	82.38± 0.98	6.58± 0.21	12.90± 0.96	17.95± 0.59	12.11± 0.33	6.73± 0.16	10.58± 0.53
1	79.77± 0.13	79.62± 0.47	20.89± 1.24	16.55± 1.56	20.85± 0.64	21.65± 0.86	11.64± 0.58	12.34± 0.42
2	75.91± 0.27	72.98± 0.21	26.67± 0.52	22.01± 0.68	28.93± 0.21	25.23± 0.92	16.21± 1.35	20.74± 0.21
3	69.56± 0.21	68.65± 0.85	57.98± 0.69	29.56± 0.26	39.66± 0.35	30.69± 0.50	39.97± 1.09	25.52± 0.85
4	64.03± 0.35	60.91± 1.74.	29.88± 0.53	35.0± 0.72	42.34± 0.78	42.24± 0.61	32.78± 0.94	27.96± 0.75
5	61.88± 0.53	56.98± 0.34	40.69± 0.62	40.21± 1.03	49.98± 0.85	50.31± 1.66	45.11± 0.48	35.24± 0.64
6	57.10± 0.42	55.45± 0.73	43.66± 0.84	45.87± 0.31	51.28± 0.13	55.82± 0.23	52.54± 0.28	37.99± 0.36
7	53.33± 0.51	52.75± 0.44	49.08± 0.45	48.33± 0.52	55.08 ±0.22	63.75± 1.26	59.42± 0.43	46.68± 1.85
8	47.79± 63	44.78± 0.12	60.13± 0.16	52.41± 0.43	62.63± 1.52	68.03± 0.75	64.88± 0.11	50.88± 0.60
9	41.12± 0.32	47.92± 0.82	64.90± 0.74	55.97± 0.20	70.10± 0.26	72.97± 0.82	70.80± 0.52	59.06± 0.59
10	34.64± 0.47	39.46± 0.56	66.12± 1.05	58.33± 0.43	72.59± 0.74	75.24± 1.89	75.03± 1.46	69.33± 1.77
11	25.79± 0.52	35.85± 0.79	68.35± 0.32	62.25± 0.44	75.11± 1.25	78.02± 0.33	79.45± 0.23	72.10± 0.34
12	21.58± 0.72	32.97± 0.45	73.99± 0.98	67.33± 0.62	79.91± 0.69	81.70± 1.06	85.64± 0.11	75.88± 0.39
16	15.26± 0.29	26.35± 0.62	76.85± 0.81	73.99± 0.56	84.25± 0.78	83.99± 0.92	94.89± 0.98	77.71± 1.22
24	9.05± 0.87	15.89± 0.42	79.54± 0.75	77.46± 0.48	87.72 ±1.64	86.95± 0.41	24.45± 0.86	81.27± 1.34

CONCLUSION

The Nanosponge drug delivery system is a boon in the area of targeted and site specific drug delivery system. In this study, Glipizide loaded Nanosponges has been developed and characterized which exhibited many features such as low dosing frequency, solubility enhancement and sustained release of drug. Glipizide loaded Nanosponges have been prepared using Emulsion solvent evaporation method by the use of Ethyl cellulose as polymer, PVP and DCM as stabilizers.

Hence, it can be concluded that it is possible to design Glipizide loaded Nanosponges for the treatment of type II diabetes where efficacy and patient compliance are of prime importance.

Future Scope

The aging population, the high expectation for better quality of life and the changing lifestyle call for improved, more efficient and affordable health care. Future areas of importance include the potential clinical application of pharmacokinetic of nanosponges, so that one could obtain an optimal dosage regimen and clinical management of individual patient and therapeutic drug monitoring.

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