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Formulation and *in vitro* Evaluation of Glipizide Nanosponges

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ABSTRACT

In this study Nanosponges were prepared by the solvent evaporation technique and subsequently formulated in a tablet form of Glipizide. The Nanosponges formulations were prepared by solvent evaporation method employing β-Cyclodextrin, HP-β Cyclodextrin and HPMC K4M as 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, production yield, and drug entrapment efficiency of Nanosponges were examined. Shape and surface morphology of the Nanosponges 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 Nanosponges in all variations; however, at higher ratios, drug crystals were observed on the nanosponge surface. Increase in the drug/polymer ratio (1:0.5 to 1:1.5) 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 average particle size of all formulations ranges from 316.4 nm to 454.8 nm. The drug content of different formulations was found in the range of 82.8to 97.2% the entrapment efficiency of different formulations were found in the range of 86.24 to 96.88%, the drug release of the Optimized formulation was found to be 99.42%.

Keywords: Glipizide**,** B-Cyclodextrin, Nanosponges Delivery System (NDS), Scanning Electron Microscopy (SEM), UV Spectroscopy.

1. INTRODUCTION

Nanosponges are novel class of hyper-crosslinked polymer based colloidal structures consisting of solid nanoparticles with colloidal sizes and nanosized 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 nanosponge is 50nm-100nm [1-5]. This technology is being used in cosmetics, over-the-counter skin care, sunscreens and prescribed drugs. Conventional formulation of topical drugs accumulates excessively in epidermis and dermis. Nanosponge prevents the accumulation of active ingredient in dermis and epidermis. Nanosponge system reduce the irritation of effective drug without reduce their efficacy [6-8].

Nanosponges are a new class of tiny sponges that are about the size of a virus, filling them with a drug and attaching- special chemical "linkers" that bond preferentially to a feature found only on the surface of tumour cells and then injecting them into the body. These tiny sponges circulate around the body until they encounter the surface of a tumour cell where they stick on the surface (or are sucked into the cell) and begin releasing their potent drug and begin releasing their potent drug in a controllable and predictable fashion [9-13].

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 [14]. Nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core [15]. As compared to

other nanoparticles, nanosponges are insoluble in water and organic solvents, porous, non toxic and stable at high temperatures up to 300^{0}C.

Nanosponges offers enhanced product performance; extended release; reduced irritation and hence improved patient compliance; improved product elegancy; oil control: It can absorb oil up to 6 times its weight without drying; improved formulation flexibility; improved thermal, physical, and chemical stability; flexibility to develop novel product forms; These are also non-irritating, non-mutagenic, non-allergenic and non-toxic.

2. MATERIALS AND METHODS

2.1 Materials

Glipizide donated by HETERO Labs Ltd. Hyderabad. Polyvinyl alcohol (PVA),HPMC K4M, HP β cyclodextrin, were obtained from Spectrum Labs Hyderabad, and other excipients were procured from colorcon, Goa.

2.2 Pre-formulation studies

2.2.1 Solubility studies

Solubility of Glipizide was carried out in different solvents like- distilled water, 0.1 N HCL & 6.8 pH buffer.

2.3 Determination of absorption maximum (λ_{max})

Accurately weighed 10mg Glipizide separately was dissolved in 10 ml of methanol 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 methanol 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 methanol 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).

2.4 Construction of calibration curve

Accurately weighed 10mg glipizide was dissolved in methanol 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 methanol 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 methanol buffer to obtain a concentration of 2, 4, 6, 8, 10 and 12µg/ml respectively. The absorbance of each solution was measured at 238nm.

2.5 Drug excipient compatibility study

The drug and excipient compatibility was observed using Fourier Transform – Infra Red spectroscopy (FT-IR).

2.6 Method of Preparation of Nanosponges

Nanosponges using different proportions of β-cyclodextrin ,HP β-cyclodextrin ,HPMC KMas rate retarding polymer and co-polymers like polyvinyl alcohol were prepared by solvent evaporation method. Disperse phase consisting of Glipizide (1gm) and requisite quantity of PVA dissolved in 10 ml solvent (ethanol) was slowly added to a definite amount of PVA in 100ml of aqueous continuous phase, prepared by using microwave oven. The reaction mixture was stirred at 1000 rpm for three hours on a magnetic stirrer. The nanosponges formed were collected by filtration through whatman filter paper and dried in oven at 50oC for 2 hours. The dried nanosponges were stored in vaccum desicator to ensure the removal of residual solvent.

2.7 Evaluation parameters of Nanosponges

The Nanosponges were evaluated for various parameters:

Drug content uniformity
Entrapment efficiency
Scanning electron microscopy
Particles size and shape
In-vitro drug release studies
Drug release kinetics studies

2.8 Evaluation of formulations

2.8.1 Drug content uniformity

40mg of the Glipizide weight equivalent was taken and dissolved in 10 ml isotonic solution and kept overnight. The dilutions were filtered and analyzed using UV for their content uniformity. The absorbance of the formulations were read using one cm cell in a UV-Vis spectrophotometer. The instrument was set at drugs wavelength (nm). The drug content in each formulation was calculated based on the absorbance values of known standard solutions.

2.8.2 Entrapment efficiency

The 40mg of the Glipizide weight equivalent nanosponge suspension 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 238nm (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.

$$\% \text{ of Drug entrapment} = \frac{\text{Mass of drug in nanosponge}}{\text{---------- (total mass of drug)}} \times 100$$

Mass of drug used in formulation

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

2.10 Particle size and shape
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.

2.11 Dissolution study
The in vitro drug release studies for the prepared formulation were conducted for a period of 12 hrs using an LAB INDIA DS8000 model dissolution tester USP Type-1 apparatus (rotating basket) set at 50 rpm and a temperature of 37± 0.5°C weight equivalent to 40mg of glipizide nanosponge was taken 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 238nm for the presence of model drug, using a UV-visible spectrophotometer.

2.12 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 glipizide from the matrix tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models.

3. RESULTS AND DISCUSSION

3.1 Solubility
Solubility of Glipizide was carried out in different solvents like- distilled water, 0.1N HCL and 6.8 pH buffer.

3.2 Determination of absorption maximum (λmax)
Determination of Glipizide λ-max was done in 6.8 pH phosphate buffer for accurate quantitative assessment of drug dissolution rate. The maximum absorbance of the glipizide in pH 6.8 buffer was found to be 238nm.

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

3.4 Drug excipient compatibility
Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. 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.

3.5 Particle size analysis of Nanosponges
The particle size of the nanosponge was determined by optical microscopy and the nanosponges were found to be uniform in size. The average particle size of all formulations ranges from 316.4 nm to 454.8 nm.

3.6 Morphology determination by scanning electron microscopy (SEM)
It was observed that the nanosponges were spherical, and uniform with no drug crystals on the surface. The shape of the nanosponges affects the surface area and surface area per unit weight of spherical nanosponges. The irregular shape of the particles may affect dissolution rate present in dissolution environment.

3.7 Drug content
The drug content of the formulated Nanosponges (F1-F9) was found in the range of 82.8to 97.2% respectively.

3.8 Entrapment Efficiency
The entrapment efficiency of formulation F1 was found to be 90.86%, formulation F2 was found to be 95.12%, formulation F3 was found to be 89.54%, formulation F4 was found to be 89.16%, formulation F5 was found to be 92.02%, and formulation F6 was found to be 86.24%, formulation F7 was found to be 92.84%, formulation F8 was found to be 96.88%, and F9 was found to be90.12 %. Among all the formulations F8 shows high entrapment efficiency of 86.88%.

3.9 *In vitro* dissolution studies of prepared nanosponges
By comparing the above dissolution studies it was clearly observed that the drug was released upto 99.42% by the end of 12 hours by F8 formulation containing HPMC K4M (1:1) shows maximum drug release at the end of 12hrs , so it was taken as the optimized formulation.The drug release kinetics were performed for the optimized formulation.

3.10 Kinetics Analysis for F8
The optimized formulation **F8** has coefficient of determination (R^2) values of 0.970, 0.731, 0.966 and 0.768 for Zero order, First order, Higuchi and 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 1.291 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.

Table 1: Formulation table of Glipizide loaded nanosponges.

S. No.	Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Glipizide (gm)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
2	PVA (gm)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3	β-cyclodextrin (gm)	0.5	1.0	1.5	--	--	--	--	--	
4	HPβ Cyclodextrin	--	--	--	0.5	1.0	1.5	--	--	--
5	HPMC K 4M	--	--	--	--	--	--	0.5	1.0	1.5
6	Ethanol (ml)	10	10	10	10	10	10	10	10	10
7	Water	100	100	100	100	100	100	100	100	100

Table 2: Particle size of Nanosponges

S. No.	Formulation code	Particle size (nm)	Drug content	Entrapment efficiency %
1	F1	321.6	88.22	90.86
2	F2	398.2	94.6	95.12
3	F3	318.2	90.	89.54
4	F4	332.4	85.2	89.16
5	F5	407.2	89.5	92.02
6	F6	329.6	82.8	86.24
7	F7	396.4	92.6	92.84
8	F8	454.8	97.2	96.88
9	F9	316.4	90.8	90.12

Table 3: Cumulative % drug release of Nanosponges

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	15.42	12.46	9.12	25.56	16.24	5.89	21.54	12.54	9.54
2	27.29	23.48	12.71	35.50	24.21	10.16	34.86	23.16	18.26
3	46.62	34.28	26.63	44.49	30.62	18.87	42.86	34.41	26.12
4	53.04	42.12	38.12	52.02	37.48	24.05	51.92	43.39	32.86
5	60.78	50.16	44.68	63.30	43.18	29.57	60.84	55.58	40.84
6	71.82	58.06	50.54	74.39	49.22	35.06	77.22	67.70	49.88
7	77.94	67.82	62.24	85.50	56.47	40.89	86.84	71.80	56.26
8	85.92	79.68	73.26	92.26	62.82	49.48	92.12	79.18	64.12
9	92.96	87.24	78.12	97.70	78.54	52.87	96.86	83.32	70.18
10	98.12	96.12	83.36		84.16	60.40	99.84	87.75	77.94
11		99.56	89.90		92.94	67.11		94.40	82.18
12			92.14			75.26		99.42	89.92

4. CONCLUSION

The Nanosponges was prepared by solvent evaporation method using βcyclodextrin, HP- βcyclodextrin, and HPMC K4M as rate retarding polymers and PVA as co polymer using ethanol as a solvent. The prepared nanosponges were evaluated for its different parameters which revealed many interesting results for efficient preparation of the nanosponge. The formulation F8 has better results than other eight formulations. F8 have its particle size 454.8nm, entrapment efficiency 96.88%, Drug content 97.2**%** drug release 99.42 % in 12 hour, all these parameters are in optimized range for preparing a sustained release dosage form so showing itself as an optimized formulation in this work.

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