JPSR (2021), Volume 12, Issue 4 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 April 2020; received in revised form, 30 January 2021; accepted, 22 March 2021; published 01 April 2021

DEVELOPMENT, OPTIMIZATION AND *IN-VITRO* CHARACTERIZATION OF GLICLAZIDE NANOSPONGE TABLETS FOR ORAL ADMINISTRATION

Shweta S. Gedam * and Ganesh D. Basarkar

SNJBS Shriman Sureshdada Jain College of Pharmacy, Chandwad, Nashik - 423101, Maharashtra, India.

Keywords:

Gliclazide, Nanosponges, Emulsion solvent diffusion method, Immediate release drug delivery, Factorial design.

Correspondence to Author:
Mrs. Shweta S. Gedam

SNJBS Shriman Sureshdada Jain College of Pharmacy, Chandwad, Nashik – 423101, Maharashtra, India.

E-mail: shwetashahare16@gmail.com

ABSTRACT: Poor bioavailability by the oral route is noticeable with the majority of new active pharmaceutical ingredients due to its dissolution rate-limited absorption. Gliclazide is an oral anti-hyperglycemic drug, though it is a class II drug, results in poor oral bioavailability. The present investigation was undertaken to prepare polymeric nanosponges of an oral anti-hyperglycemic drug Gliclazide to achieve improved solubility. Nanosponges using ethyl cellulose as a polymer and glutarldehyde as a cross-linker were prepared successfully by the emulsion solvent diffusion method. Drug polymer compatibility study was performed by FTIR and DSC. To obtain optimized batch, 32 factorial designs were performed. Optimized batch exhibited particle size 398. 78 nm, % drug content 90.504 ± 0.296, % entrapment efficiency 81.25 ± 0.266, % drug release 97.725 ± 0.186. An SEM and TEM image of optimized batch shows the spongy and spherical nature of formulations were converted into tablets to achieve immediate release drug delivery for oral route. These tablets were prepared using crospovidone and A SEM and TEM image of the optimized batch shows spongy and spherical nature of nanosponges pregelatinized starch. All nine tablet batches of 32 factorial design yield sharpness (kg/cm^{-2}) between 3.76 ± 0.115-4.2 ± 0.1, % friability between 0.4191-0.5571, drug content 98.41 ±1.1331-99.40 ± 0 .741, *in-vitro* disintegration time (min) 0.44 ± 0.043-1.4 ± 0.047 and % drug release between 83.803 ± 0.1866-98.269 ± 0.187. (kg/cm2) 4.03 ± 0.057, *in-vitro* disintegration time (min) 0.44 ± 0.043 and % drug release 98.269 ± 0.187. *In-vitro* dissolution studies indicate that percent cumulative drug release follows zero-order kinetics. Accelerated and long-term stability data revealed no significant change in % drug content and percent drug release.

INTRODUCTION: Diabetes mellitus is a major health problem and an important cause of prolonged ill health and early death. Type 2 diabetes is the most common form of diabetes mellitus, accounting for approximately 90% of cases and affecting about 100 million people in the world. The projection indicates that there will be over 450 million type 2 diabetic patients by the year 2030. Diabetes mellitus is a metabolic disorder in which prolonged treatment is necessary. An ideal anti-diabetic drug would be the one that not only does control the glycemia level but also prevents the development of complications [1].

Oral hypoglycemic agents like sulphonylureas are the major players in the management of type 2 diabetes. Gliclazide, a second-generation sulphony lurea, is preferred in the therapy because of its selective inhibitory activity towards pancreatic K+ ATP channels, unique antioxidant properties, and other beneficial haemobiological effects.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(4).2158-74

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(4).2158-74

It is BCS class II drug having low bioavailability due to extensive first-pass hepatic metabolism and binding to plasma protein (94%) reduces its aqueous solubility [2]. Advances in the *in-vitro* screening process of newly synthesized chemical moiety lead to the emergence of many challenging chemical components with noticeable therapeutic activity. However, about 40% of them are poorly water-soluble drugs that have low oral bioavailability as their absorption is dissolution rate limited [1]. Apart from this, major drawbacks of oral drug delivery of these drugs suffer from rapid metabolism, lack of steady-state blood/plasma concentration of the drug, and inter-individual variability [2]. 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 nanometers 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 [3]. 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 [3].

MATERIALS AND METHODS:

Materials: Gliclazide was obtained as a generous gift sample from Wockhardt Pharmaceutical Ltd., Aurangabad. Ethylcellulose, glutaraldehyde, and polyvinyl alcohol, lactose anhydrous, avicel 101, crospovidone, pregelatinized starch, magnesium stearate were purchased from Research-lab Fine Chem industries. All other chemicals and reagents used were of analytical reagent grade and were procured from commercial sources.

Methodology:

Calibration Curve by U. V. Visible Spectro-photometric Method: Calibration curve in methanol and phosphate buffer pH 7.4. were performed by U. V. Visible Spectrophotometer (Agilent carry-60) [4].

Drug-polymer Compatibility study:

Fourier-Transform Infrared Spectroscopy: Fourier-transform infrared (FTIR) spectra of pure Gliclazide, pure polymer (EC), physical mixture of Gliclazide &ethyl cellulose, and nanosponges of drug Gliclazide was taken to access interaction if any between drug and polymer in mixtures. The mixture was scanned by using an FTIR spectro-photometer (Perkin Elmer, Spectrum 2 FTIR) [5].

Differential Scanning Calorimetric: Differential scanning calorimetric (DSC) studies of pure Gliclazide, pure polymer (EC), physical mixture of Gliclazide & ethylcellulose, and nanosponges of drug Nateglinide was performed by Differential Scanning Calorimeter with thermal analyzer Metller Star SW 10.6.

Preparation of Nanosponges: Nanosponges were prepared by the emulsion solvent diffusion method by using two phases, *i.e.*, organic and aqueous. The aqueous phase was prepared by dissolving a definite amount of PVA in water by continuous stirring on a water bath. After dissolving the drug and polymer to suitable organic solvent, this phase was sonicated for a few minutes and added slowly to the aqueous phase under stirring. The resultant nanosponges were collected by filtration, washed with water, and kept for drying in the oven. The nanosponges were then packed and stored in airtight vials for further study [7].

Optimization of Nanosponge Formulation Utilizing 32 Factorial Design: A 3^2 full factorial design was constructed to study the effect of two independent variables at three levels. Analysis of variance (ANOVA) was performed to study the statistical significance of independent variables and their interaction term. Polynomial equations were calculated for responses. Design expert (version 8.0.4.1) was used for the statistical and mathematical analysis [8, 9].

TABLE 1: SHOWING TWO INDEPENDENT VARIABLES AT 3 LEVELS

Factor	Level		
	Low (-1)	Medium (0)	High (+1)
X1: Drug: polymer ratio (mg)	1:0.75	1:1	1:1.25
X1: Volume of glutarldehyde (ml)	5	10	15

TABLE 2: SHOWING THREE DEPENDENT VARIABLES

Responses	
Y_1	Particle size (nm)
Y_2	Drug content %
Y3	*In vitro* drug release (%)

Evaluation of Nanosponges:

Particle Size and Polydispersity: The particle size and polydispersibility index (PDI) was determined by Malvern Zeta sizer. PDI is an index of width or spread, or variation within the particle size distribution[7].

Product Yield: The percent yield of microsphere was calculated based on the amount of drug and polymer used for the formulation of nanosponges [8]. The percentage yield was calculated from the following equation,

Product Yield = Practical mass Nanosponges / Theoritical mass (Polymer + drug) × 100

Percent Entrapment Efficiency (%): 10 mg equivalent of Gliclazide nanosponges were dissolved in 10 ml of methanol. The absorbance was measured by UV- visible spectrophotometer (Agilent carry-60) at 227 nm [8]. The % entrapment efficiency was followed,

Loding Efficiency = Actual Drug Content in Nanosponges / Weighted quantity of powder of Nanosponges × 100

Percent Drug Content: To calculate the drug content, accurately weighed quantity of nanosponges (10 mg) with 5 ml of methanol in a volumetric flask was shaken for 1 min using vortex mixer. The volume was made up to 10 ml. Then the solution was filtered and diluted, and the concentration of Gliclazide was determined spectro metrically at 230 nm [3].

Drug Content = Actual Drug Content in Nanosponges / Theoretical Drug Content × 100

TABLE 3: FORMULATION FOR GLICLAZIDE NANOSPONGES

Batches	Drug: Ethyl cellulose ratio (mg)	PVA conc. (mg)	Glutaraldehyde (ml)	Distilled water (ml)
G1	1:0.75	0.3	05	100
G2	1:1	0.3	05	100
G3	1:1.25	0.3	05	100
G4	1:0.75	0.3	10	100
G5	1:1	0.3	10	100
G6	1:1.25	0.3	10	100
G7	1:0.75	0.3	15	100
G8	1:1	0.3	15	100
G9	1:1.25	0.3	15	100

***In-vitro* Release Studies:** *In-vitro* release studies were performed in triplicate using USP Paddle method at 100 rpm and 37 ± 0.5 °C in 900 ml of Phosphate buffer pH 7.4. Samples were taken at appropriate time intervals of 5min. for a period of 45 min. The filtered samples were analyzed spectro-photometrically at 224 nm [3].

X-Ray Diffraction Studies: XRD studies of drug Gliclazide and Gliclazide nanosponges were recorded using X-ray diffract to a meter (Make Bruker, Model D8 Advance, with X-ray source of Cu, Wavelength 1.5406 A0 and Si (Li) PSD detector). Which was operated at the current and voltage of 40 kV and 40 mA respectively.

These studies are useful to investigate the changes in the crystallinity of drugs and nanosponges. The samples were smeared over a low background sample holder, and XRD patterns were recorded in the 2θ geometry and step 0.020 size at the speed of 5°/min [10].

Scanning & Transmission Electron Microscopy: Nanosponges that showed the best results (G5) were subjected to scanning & transmission electron microscopy (SEM & TEM) studies. Images were recorded at the required magnification at an acceleration voltage of 20 KV using a scanning electron microscope [10].

Preparation of Immediate Release Tablets Using Direct Compression Method: The weighted quantity of nanosponges equivalent to 40mg of the drug was taken. The excipients were passed through #60-sieve. All these ingredients except magnesium stearate were mixed in a double cone blender (Orchid, AP-01) for 10 min at 10 rpm. Sifted magnesium stearate was then added to the blend and mixed in the double cone blender for

another 2 min. The blend was compressed using 12 station Tablet press (Accura mini R & D model) using 8 mm circular flat beveled edge punches [11].

Optimization of Tablet Formulation Utilizing 3^2 Factorial Design: A 3^2 full factorial design was constructed to study the effect of two independent variables at three levels.

Analysis of variance (ANOVA) was performed to study the statistical significance of independent variables and their interaction term.

Polynomial equations were calculated as responses. Design expert (Version 8.0.4.1) was used for the statistical and mathematical analysis [8].

TABLE 4: SHOWING TWO INDEPENDENT VARIABLES AT 3 LEVELS

Factor	Level		
	Low (-1)	Medium (0)	High (+1)
X1: Conc. of superdisintegrant (mg)	4.5	5.62	6.75
X2: Conc. of binder (mg)	4.5	7.5	10.5

Pre-compression Evaluation of Powder:

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 [12]. Bulk density was calculated as,

Bulk density = Mass (gm) / 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 [12].

Tapped density = Mass (gm) / 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 [13].

CI (%) = [(Tapped density - Bulk density) / Tapped density] × 100

Hausner's Ratio: It provides an indication of the degree of densification, which could result from the vibration of feed hopper [14].

HR = Tapped density / 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 [14]. Angle of repose was calculated from the average radius using the following formula.

$$\tan \theta = h/r; \ \theta = \tan^{-1} h/r$$

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

TABLE 5: SHOWING THREE DEPENDENT VARIABLES

Responses	
Y_1	Hardness (kg/cm^2)
Y_2	Disintegration (min)
Y3	*In vitro* drug release (%)

TABLE 6: FORMULATION FOR GLICLAZIDE NANOSPONGES TABLETS

Batches	Gliclazide nanosponges	Lactose anhyd. NF	Crospovidone IP	Pregelatinised starch (mg) IP	Talc IP	Magnesium stearate IP	Total weight (mg)
F1	44.1[9]	92.81	4.5	4.5	2.5	1.5	150
F2	44.19	91.69	5.62	4.5	2.5	1.5	150
F3	44.19	90.56	6.75	4.5	2.5	1.5	150
F4	44.19	89.81	4.5	7.5	2.5	1.5	150
F5	44.19	88.69	5.62	7.5	2.5	1.5	150
F6	44.19	87.56	6.75	7.5	2.5	1.5	150
F7	44.19	86.81	4.5	10.5	2.5	1.5	150
F8	44.19	85.69	5.62	10.5	2.5	1.5	150
F9	44.19	84.56	6.75	10.5	2.5	1.5	150

Post Compression Evaluation of Gliclazide Nanosponge Tablets: All prepared tablets were evaluated for the following 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 [15].

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 [16].

% Friability = (Initial weight - Final weight)* 100 / Initial weight

Hardness: Hardness was measured using the Monsanto hardness tester [17].

Thickness: The thickness of the tablets was measured by using vernier caliper by picking the tablets randomly [17].

Drug Content: To calculate drug content, accurately weighed quantity of crushed tablet (10 mg) and 5 ml of methanol in a volumetric flask was shaken for 1 min using a vortex mixer.

The volume was made upto 10 ml then the prepared solution was filtered and diluted; the concentration of Gliclazide was determined spectrometrically at 230 nm [3].

Wetting Time Five circular tissue papers of 10 cm diameter were placed into a petridish containing 0.2% w/v solution of amaranth (10 ml).

Drug content = Actual Drug Content Nanosponges / Theoretical Drug Content × 100

One tablet was placed on the surface of the tissue. The time required to develop the blue color of amaranth solution on the side of the tablets was noted as a wetting time [18].

Wetting Time: Five circular tissue papers of 10 cm diameter were placed into a petridish containing 0.2% w/v solution of amaranth (10 ml). One tablet was placed on the surface of the tissue.

The time required to develop the blue color of amaranth solution on the side of the tablets was noted as a wetting time [18].

Water Absorption Ratio: A small piece of tissue folded twice was placed into a petridish containing 6 ml of water. A tablet was placed on the paper before the initial weight of the tablet is noted.

The wetted tablet was then weighed [18]. Water absorption ratio (R) was calculated using the following equation,

$$R = (Wa - Wb) / Wb \times 100$$

Where, W_a = Weight of the tablet after absorption
W_b = Weight of the tablet before absorption

***In-vitro* Disintegration:** *In-vitro* Disintegration test was carried out with the help of disintegration apparatus.

Tablet was placed in every tube (six) of the basket containing 900 ml of phosphate buffer pH 7.4, the temperature of immersion fluid was maintained at 37 ± 2 °C.

Apparatus was operated till no residue of the unit under test remains on the screen of apparatus [18].

***In-vitro* Dissolution Study:** *In-vitro* release studies were performed in triplicate using the USP Paddle method at 100 rpm and 37 ± 0.5 °C in 900 ml of Phosphate buffer pH 7.4.

Samples were taken at appropriate time intervals of 5 min. for a period of 45 min. The filtered samples were analyzed spectrophotometrically at 224 nm [4].

Stability Studies: Stability studies of prepared tablets were performed as per the standard protocol.

The accelerated stability studies at 40 °C ± 2 °C/75% RH ± 5% RH for a period of 6 months and at room temperature for 12 months were carried out. Samples were analyzed for (%) drug content and (%) *in-vitro* drug release [8].

RESULTS AND DISCUSSION:

UV Visible Spectrophotometric Study: Determination of λ_{max} of Gliclazide in Phosphate Buffer (pH 7.4.) and methanol

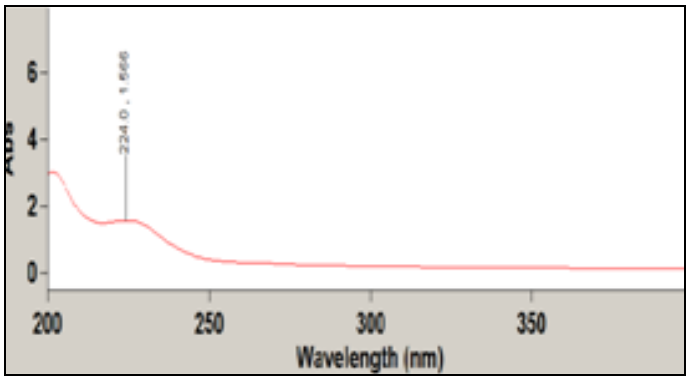


FIG. 1: UV-SPECTRA OF PURE GLICLAZIDE IN PHOSPHATE BUFFER (PH7.4)

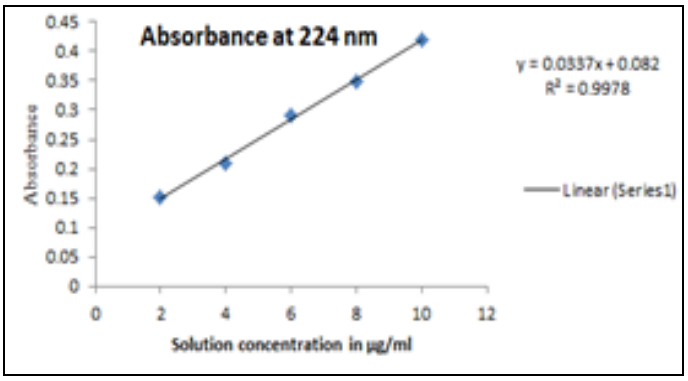


FIG. 2: STANDARD CALIBRATION CURVE OF GLICLAZIDE IN PHOSPHATE BUFFER (PH 7.4)

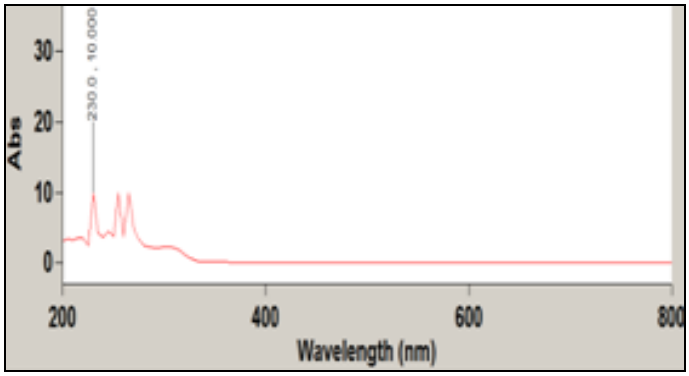


FIG. 3: DETERMINATION OFΛ MAX OF GLICLAZIDE IN METHANOL

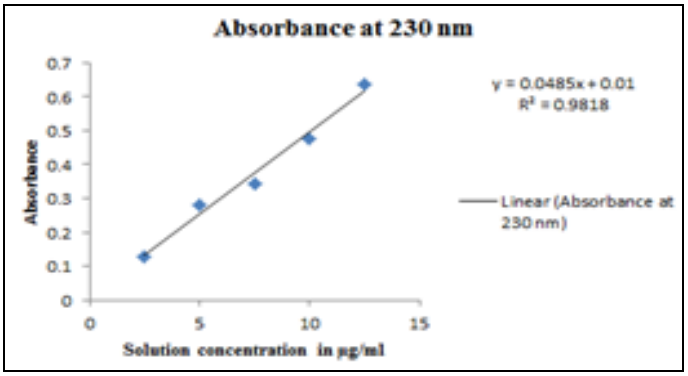


FIG. 4: STANDARD CALIBRATION CURVE OF GLICLAZIDE IN METHANOL

Fourier Transforms Infrared Spectroscopy (FT-IR) analysis:

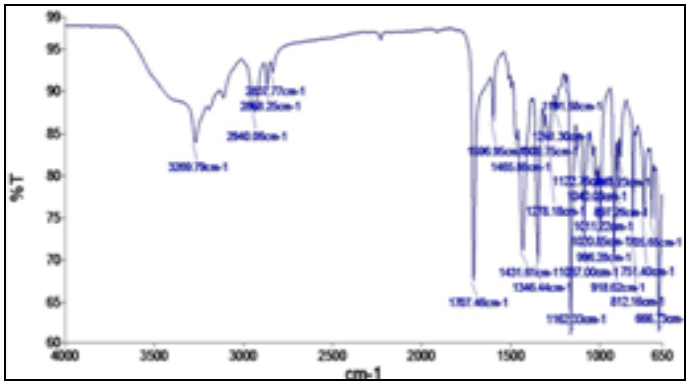


FIG. 5: FT-IRSPECTRA OF PURE GLICLAZIDE

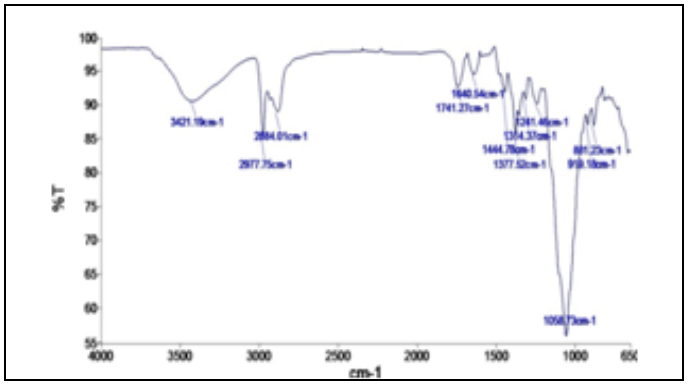


FIG. 6: FT-IR SPECTRA OF ETHYL CELLULOSE

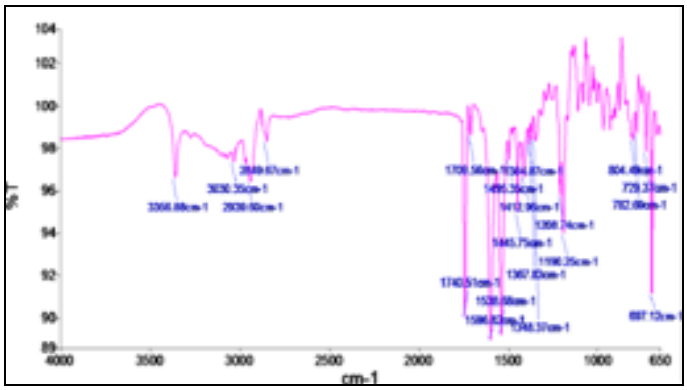


FIG. 7: FT-IR SPECTRA OF GLICLAZIDE AND ETHYL CELLULOSE (PHYSICAL MIXTURE)

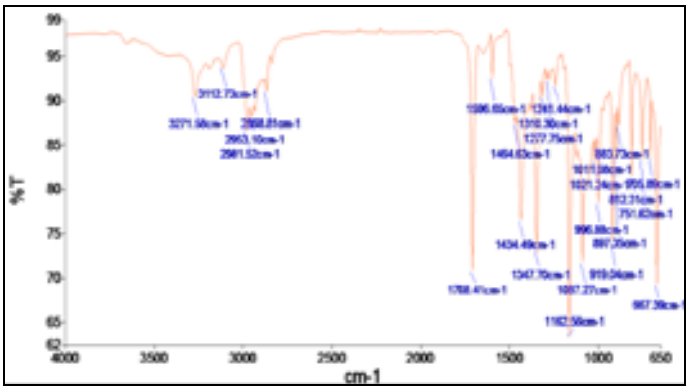


FIG. 8: FT-IR SPECTRA OF GLICLAZIDE NANOSPONGES

To check the compatibility of the drug with a polymer, infrared spectra of drug, polymers, and mixture of drug-polymer were studied by using FTIR-ATR (spectrum 2, Perkin Elmer).

All IR spectrum indicates that there is no physicochemical interaction in between the drug and polymer, which suggests that the polymer is compatible with FTIR spectra of Gliclazide.

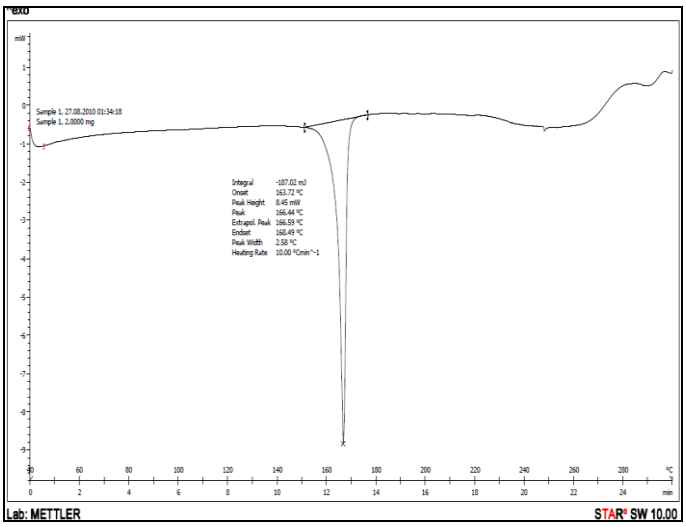


FIG. 9: DSC THERMOGRAM OF PURE DRUG GLICLAZIDE

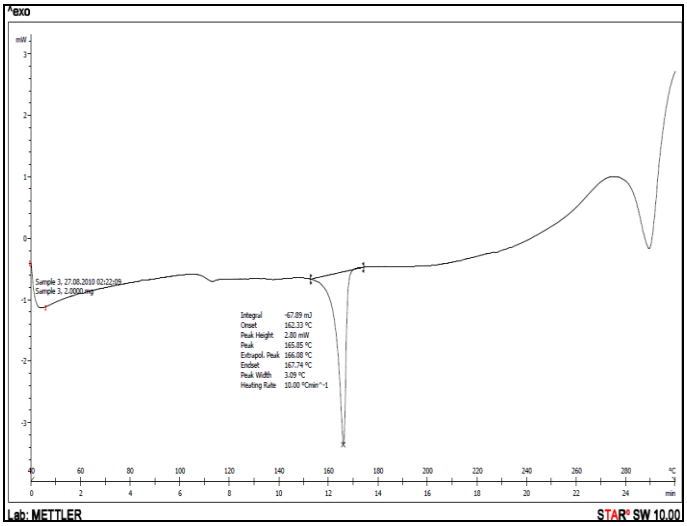


FIG. 10: DSC THERMOGRAM OF PHYSICAL MIXTURE OF PURE DRUG GLICLAZIDE AND POLYMER

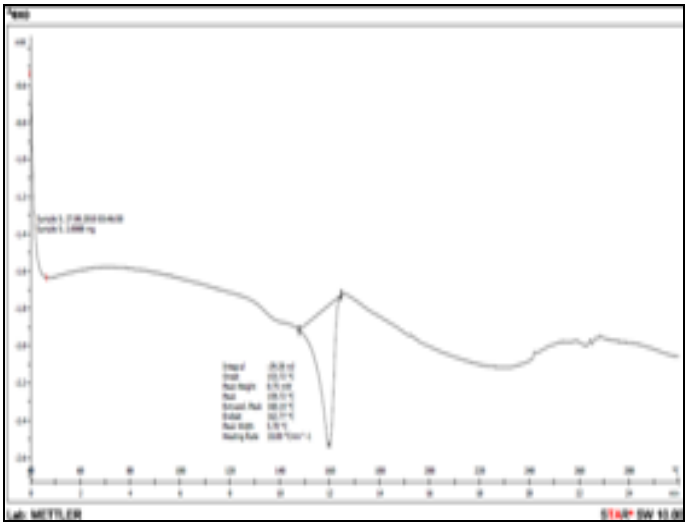


FIG. 11: DSC THERMOGRAM OF GLICLAZIDE NANOSPONGES

Differential Scanning Calorimetry: DSC curve of Gliclazide shows a sharp peak at 166.44 ºC. The pure polymer (Ethylcellulose) exhibits a peak at 70.01 ºC, referring to the relaxation that follows the glass transition. The DSC Thermogram of nanosponges shows a broad peak with reduced intensity.

The broad peak was observed because of the glassy nature of the polymer. Little shift in the melting point was observed due to the formation of weak hydrogen bonding between drug and polymer. This phenomenon is responsible for the solubility enhancement.

DSC curve of Gliclazide shows a sharp peak at 166.44 ºC. The pure polymer (Ethyl cellulose) exhibits a peak at 70.01 ºC, referring to the relaxation that follows the glass transition. The DSC Thermogram of nanosponges shows broad peak with reduced intensity.

The broad peak was observed because of glassy nature of polymer. Little shift in the melting point was observed due to formation of weak hydrogen bonding between drug and polymer. This phenomenon is responsible for the solubility enhancement.

TABLE 7: EVALUATION OF OPTIMIZED BATCHES OF GLICLAZIDE NANOSPONGES

Batches	Particle size (nm)	PDI	Product yield	Drug content	Entrapment efficiency (%)
G1	247.12	0.152	71.43%	66.469 ±0.296	47.49±0.212
G2	163.32	0.182	77.23%	78.932±0.513	58.04±0.377
G3	189.65	0.167	73.54%	71.612±0.453	55.30±0.350
G4	107.67	0.121	79.66%	74.58±0.453	60.90±0.370
G5	48.21	0.101	89.78%	90.504±0.296	81.25±0.266
G6	82.43	0.127	85.89%	82.88±0.171	71.19±1.147
G7	398.78	0.23	62.78%	55.194±0.513	34.65±0.322
G8	307.57	0.189	69.66%	64.491±0.746	44.92±0.52
G9	364.23	0.199	67.74%	59.94±0.593	40.60±0.402

The results of nanosponge evaluation are shown in **Table 7**. The particle size drug content and % entrapment efficiency were within the normal, acceptable range. For formulation G5 shows good results *i.e.*, particle size and PDI was 48.21 nm & 0.101 respectively, percent drug content (%), entrapment efficiency (%) shows good results, *i.e.*, 90.504 ± 0.296 and 81.25 ± 0.266 respectively. The optimized batch shows good percent *in-vitro* drug release 97.725 ± 0.186.

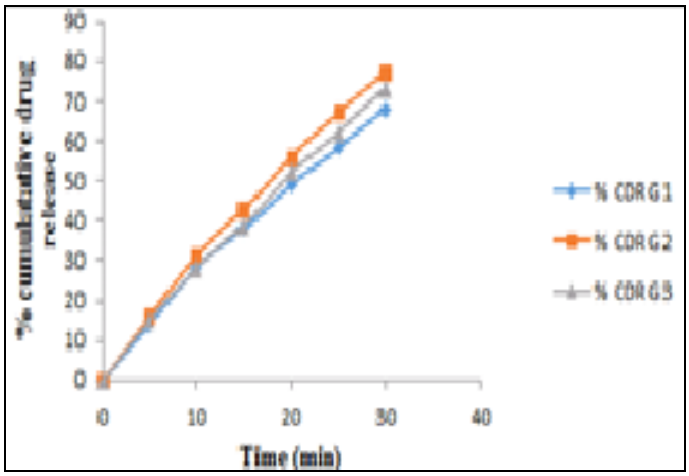


FIG. 12: % DRUG RELEASE FROM G1-G3 BATCHES

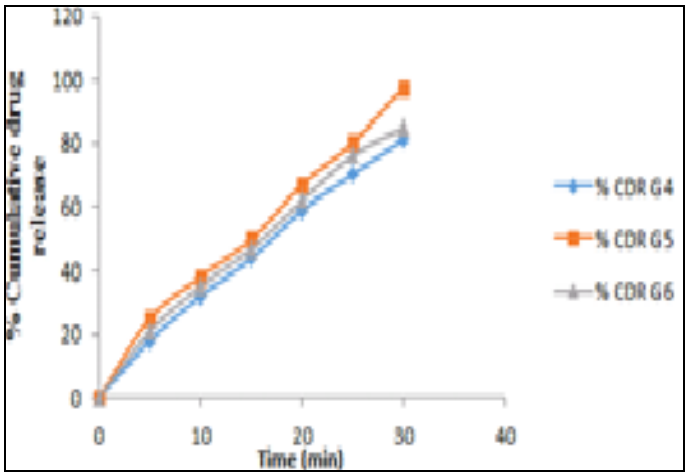


FIG. 13: % DRUG RELEASE FROM G4-G6 BATCHES

X-ray Diffraction Studies (XRD): X-ray diffraction (XRD) analysis was carried by using an x-ray diffraction (XRD) system. The x-ray diffraction (XRD) pattern for pure Gliclazide-loaded nano-sponges are shown in **Fig. 7**. Changes in the number of peaks and few diffuse peaks were observed in Gliclazide loaded nanosponges with reduced intensity to a greater extent as compared to x-ray diffraction (XRD) spectrum of the pure drug indicates it changes towards amorphous form.

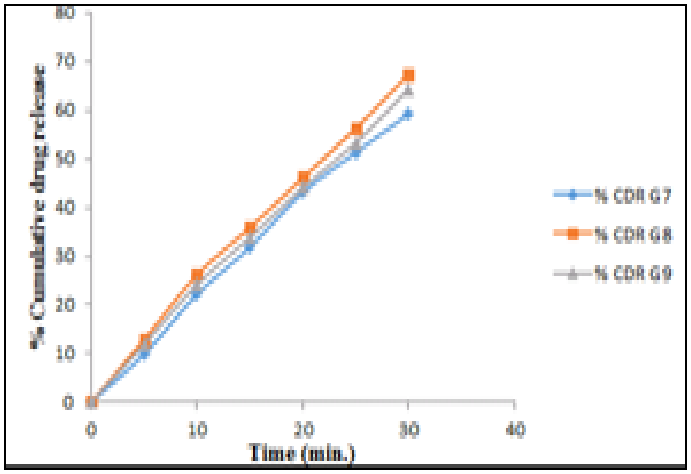


FIG. 14: % DRUG RELEASE FROM G7-G9 BATCHES

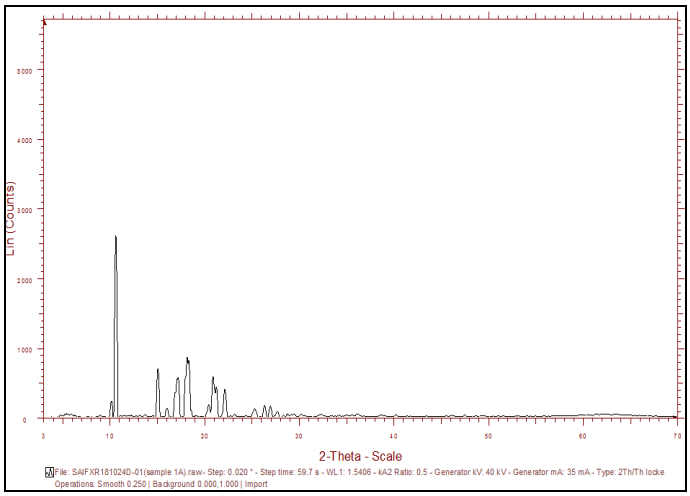


FIG. 15: XRD PATTERNS OF PURE DRUG GLICLAZIDE

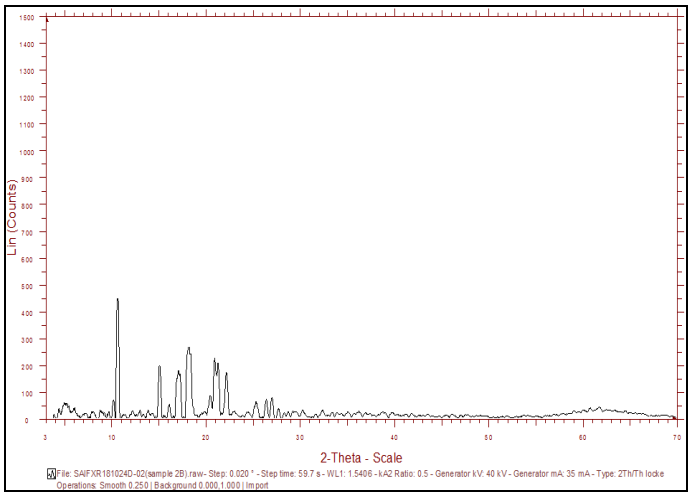
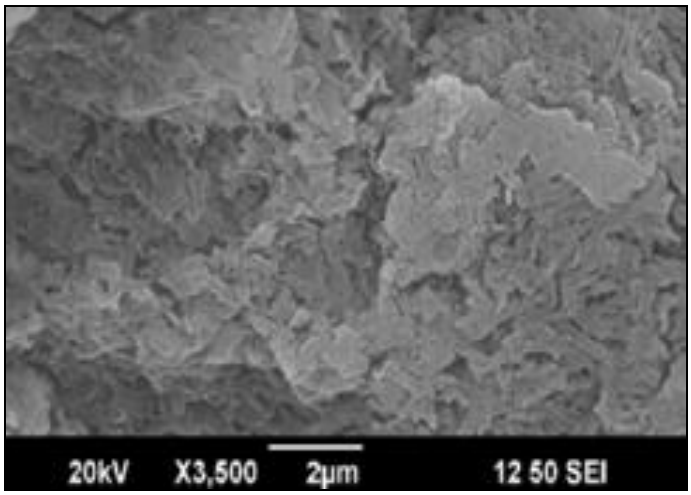


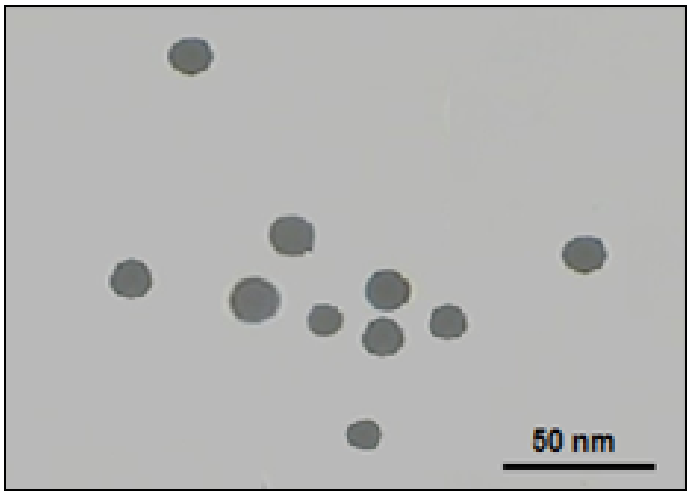
FIG. 16: XRD PATTERNS OF GLICLAZIDE LOADED NANOSPONGES

Scanning & Transmission Electron Microscopy (SEM & TEM): The morphology of the optimized batch was studied by SEM and TEM analysis, as shown in **Fig. 17**.

Zeta Potential: The negative zeta potential values *i.e.*, -17.23, data on result indicates good stability of Gliclazide nanosponges.



SEM IMAGE



TEM IMAGE

FIG. 17: SEM & TEM IMAGES OF NANOSPONGES

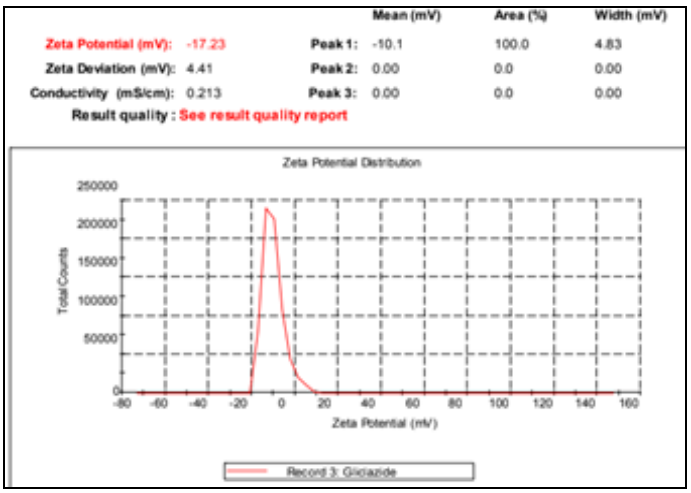
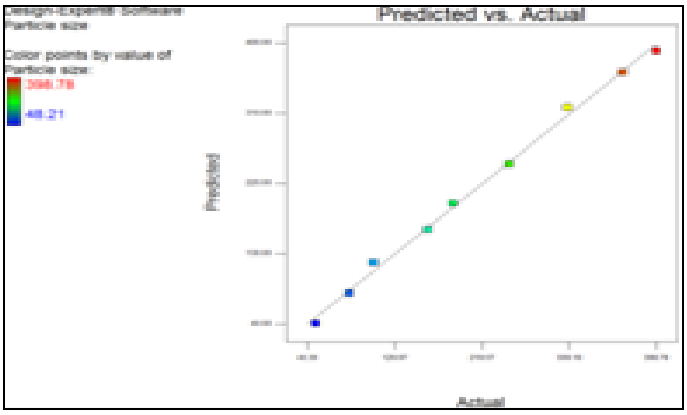
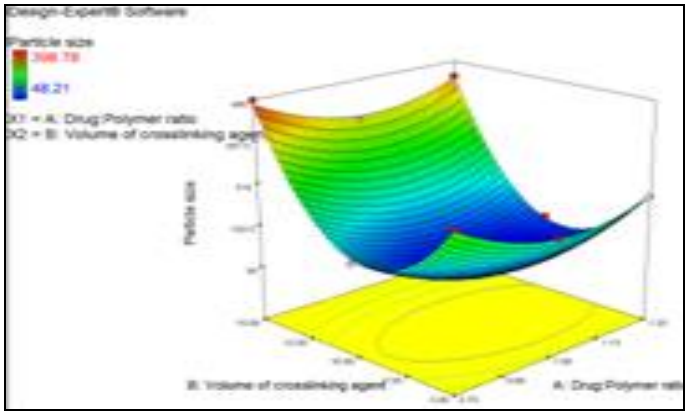


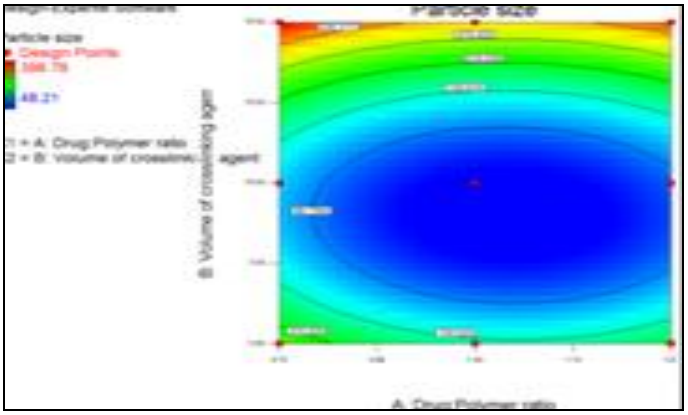
FIG. 18: ZETA POTENTIAL DETERMINATION OF GLICLAZIDE NANOSPONGES



PREDICTED V/S ACTUAL PLOT FOR PARTICLE SIZE (Y1)



3-D RESPONSE CURVE FOR PARTICLE SIZE (Y1)



COUNTER PLOT FOR PARTICLE SIZE (Y1)

3^2 Factorial Design for Optimization of Gliclazide Nanosponges:

A. For Dependent Variable – Particle Size (Y1):

Final Equation in Terms of Coded Factors: Particle size = + 40.36 -19.54 * A + 78.41 * B + 5.73 * A * B + 58.61 * A2 + 199.01* B2

Final Equationin Terms of Actual Factors: Particle size = + 1741.39111-1999.64000 * Drug: Polymer ratio-148.10767 * Volume of cross linking agent + 4.58400 * Drug: Polymer ratio *Volume of cross linking agent + 937.81333 * Drug: Polymer ratio 2 + 7.96033 *Volume of cross linking agent 2.

B. For Dependent Variable –Drug Content (Y2):

Final Equationin Terms of Coded Factors: Drug content = + 89.01+3.03 * A-6.23 * B-0.099* A * B-9.53* A2-16.55 * B2

Final Equation in Terms of Actual Factors: Drug content = -130.12011 + 317.87467 * Drug: Polymer ratio + 12.07180 * Volume of cross linking agent-0.079400 *

Drug: Polymer ratio * Volume of cross-linking agent-152.47733 *Drug: Polymer ratio2-0.66193 *Volume of cross-linking agent 2

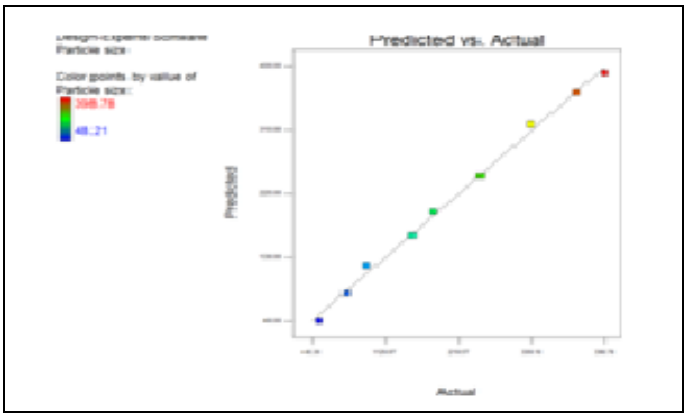
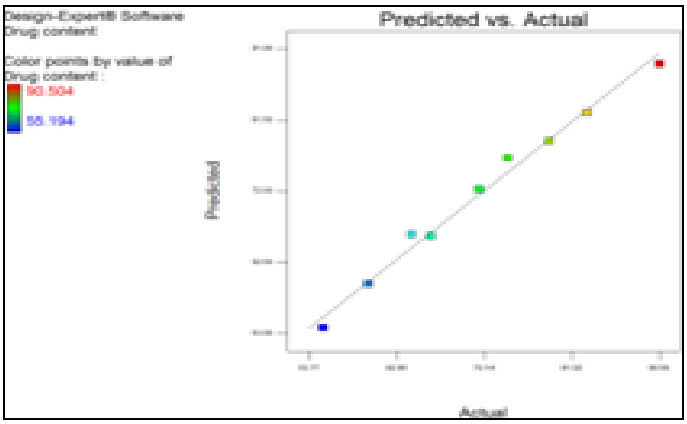
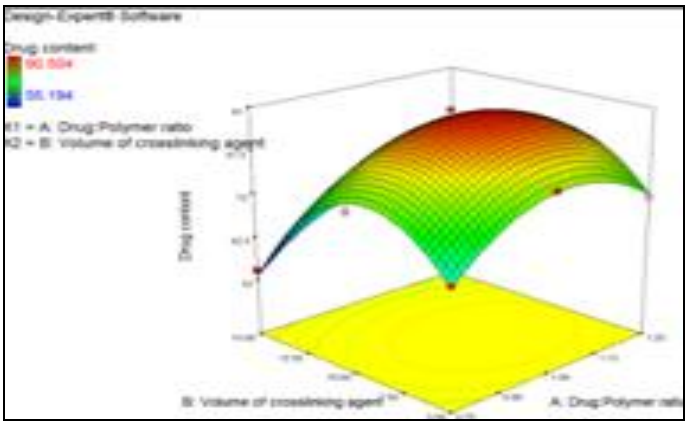


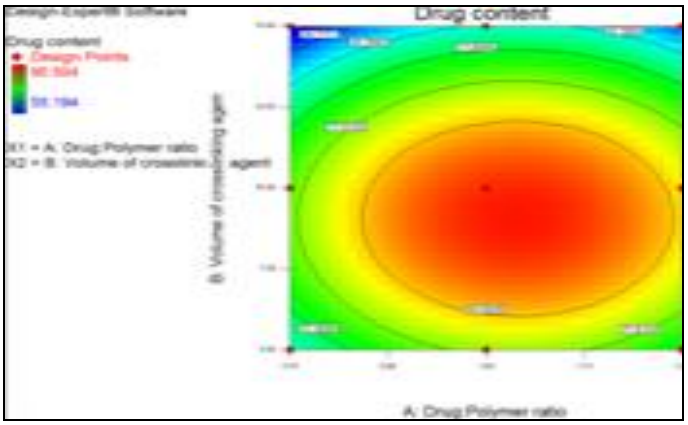
FIG. 18: ZETA POTENTIAL DETERMINATION OF GLICLAZIDE NANOSPONGES



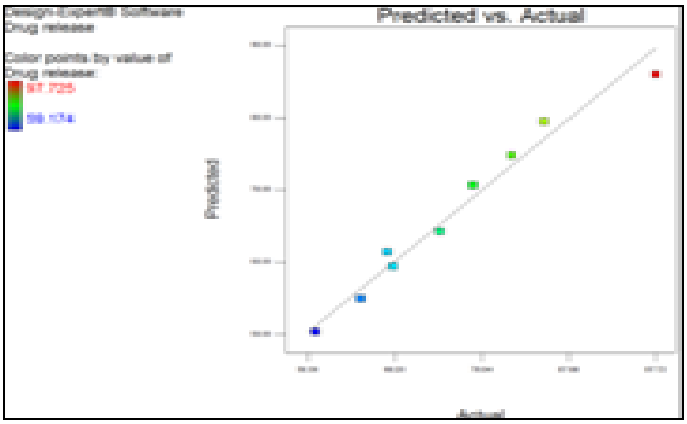
PREDICTED V/S ACTUAL PLOT FOR DRUG CONTENT (Y2)



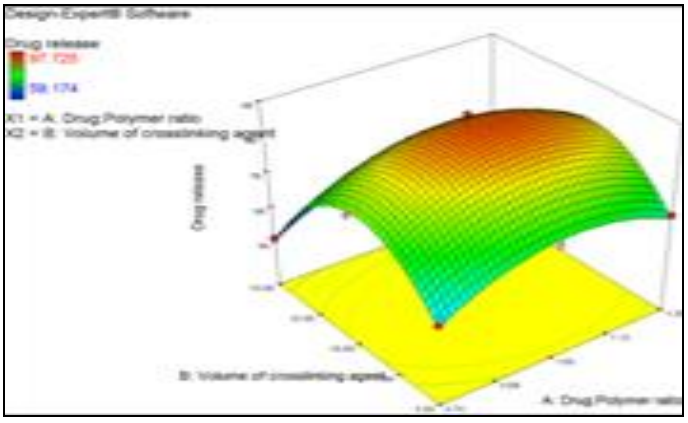
3-D RESPONSE CURVE FOR DRUG CONTENT (Y2)



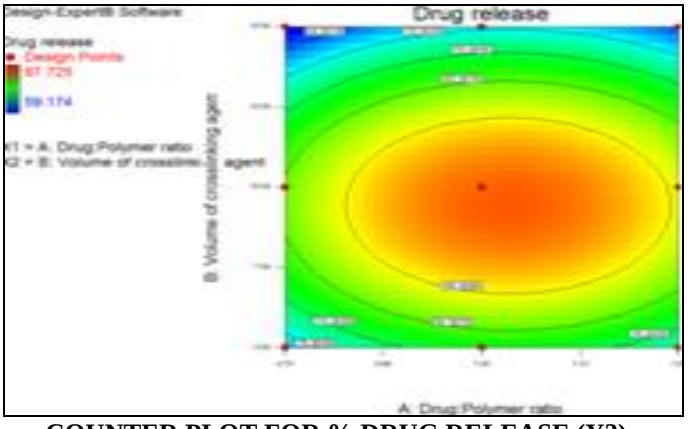
COUNTER PLOT FOR DRUG CONTENT (Y2)



PREDICTED V/S ACTUAL PLOT FOR % DRUG RELEASE (Y3)



3-D RESPONSE CURVE FOR % DRUG RELEASE (Y3)



COUNTER PLOT FOR % DRUG RELEASE (Y3)

C. For Dependent Variable – % Drug Release (Y3):

Final Equation for in Terms of Coded Factors: Drug release = + 93.96 + 2.35 * A-4.59 * B-0.043 * A * B-8.82 * A2-19.89 * B2

Final Equation in Terms of Actual Factors: Drug release = -127.21633 + 291.82267 * Drug: Polymer ratio + 15.03197 * Volume of cross-linking agent - 0.034600 * Drug: ratio * Volume of cross-linking agent - 41.04800 * Drug: Polymer ratio 2-0.79574 * Volume of cross-linking agent 2.

From the results of 3^2 factorial designs, it was found that as polymer concentration increases, particle size decreases to some extent, and then there is an increase in particle size. This may be due to that, increase in polymer concentration result in decrease cross-linking. Also, these results show that as polymer concentration increases, it shows an increase in % drug content and % drug release at some level and then decreases. As cross-linking agent concentration increases, there is a decrease in particle size to some extent, and then there is an increase in particle size.

Also, these results show that as cross-linking agent concentration increases, it shows an increase in % drug content and % drug release at some level and then decreases. From the above results, the G5 batch was selected as an optimized batch so, it was selected for tablet preparation.

Evaluation of Tablet Dosage Form:

TABLE 8: PRE-COMPRESSION EVALUATION OF OPTIMIZED BATCHES

Batch Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio(HR)	% Carr's index (CI)
F1	27.25±1.42	1.303±0.0019	1.444±0.0024	1.107362±0.0019	9.695291±0.0015
F2	25.12±0.76	1.27±0.0086	1.4378±0.002	1.107362±0.0013	9.027681±0.0273
F3	25.16±0.65	1.259±0.00317	1.386±0.0021	1.099235±0.0016	8.867244±0.0274
F4	26.31±1.23	1.304±0.0134	1.438±0.0024	1.099235±0.0019	9.72879±0.0019
F5	26.24±0.79	1.307±0.0019	1.4376±0.002	1.0973±0.0025	9.696717±0.0258
F6	25.65±1.16	1.290±0.0019	1.4267±0.002	1.107773±0.0032	8.796523±0.0239
F7	25.27±1.24	1.323±0.0020	1.4421±0.002	1.107379±0.00390	9.389085±0.018
F8	26.53±1.17	1.3077±0.0019	1.431±0.0002	1.107379±0.00310	9.287212±0.0242
F9	27.22±1.43	1.2964±0.0019	1.4473±0.002	1.096449±0.0017	9.804463±0.0743

TABLE 9: POST COMPRESSION EVALUATION OF OPTIMIZED BATCHES

Batch Code	Weight variation (Average weight in (mg) ± SD (n=10))	Hardness(kg/cm^2) ±SD (n=3)	Thickness (mm) ± SD (n=3)	Friability (%)	Drug Content Uniformity (%) ± SD (n=3)
F1	0.162±0.352	3.9±0.05	3.14±0.08	0.63	98.31±0.68
F2	0.331±0.438	3.8±0.05	3.15±0.16	0.61	99.05±1.16
F3	0.279± 0.231	3.7±0.15	3.17±0.03	0.55	99.50±1.31
F4	0.421±0.321	4.0±0.17	3.14±0.16	0.54	97.68±0.95
F5	0.141±0.165	4.0±0.15	3.15±0.01	0.57	99.65±1.40
F6	0.543±0.254	3.8±0.26	3.16±0.12	0.57	99.91±1.81
F7	0.387±0.567	4.1±0.05	3.16±0.14	0.58	98.65±0.57
F8	0.369±0.178	3.9±0.1	3.15±0.13	0.58	98.41±1.33
F9	0.243±0.431	4.0±0.17	3.14±0.13	0.52	98.56±1.42

TABLE 10: POST COMPRESSION EVALUATION OF OPTIMIZED BATCHES

Formulation Code	Wetting Time (n=3) Mean ±SD (sec)	Water Absorption ratio (n=3) Mean ±SD	*In-vitro* Disintegration Time (sec.)
F1	43±1.52	65±1.71	4.48±1.01
F2	57±1.15	58±1.23	4.26±1.02
F3	45±1.52	68±1.47	4.36 ±1.00
F4	49±1.15	60±1.52	4.24±1.01
F5	41±0.57	74±1.33	3.24±1.70
F6	46±1.15	63±1.32	3.43±1.01
F7	63±1.52	53±1.73	5. 59±1.55
F8	47±1.15	65±1.38	5.37±0.04

3^2 Factorial Designs for Optimization of Gliclazide Nanosponges Tablet:

A. For Dependent Variable –Hardness (Y1): Final Equation in Terms of Coded Factors: Hardness = + 3.91- 0.083 * A + 0.12 * B Final Equation in Terms of Actual Factors: Hardness = + 4.03611-0.074074* Conc. of Crospovidone + 0.038889 * Conc. of Pregelatinised starch. On basis of evaluation results shown in **Table 9** & **10** and **Fig. 19 and 21**, F8 batch formulation was selected as optimized batch.

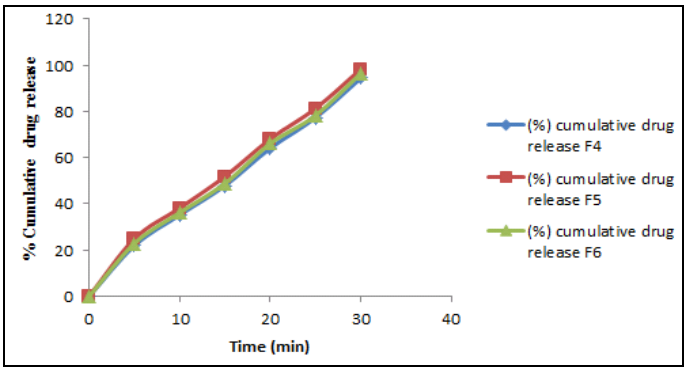


FIG. 19: % DRUG RELEASE FROM F1-F3 BATCHES

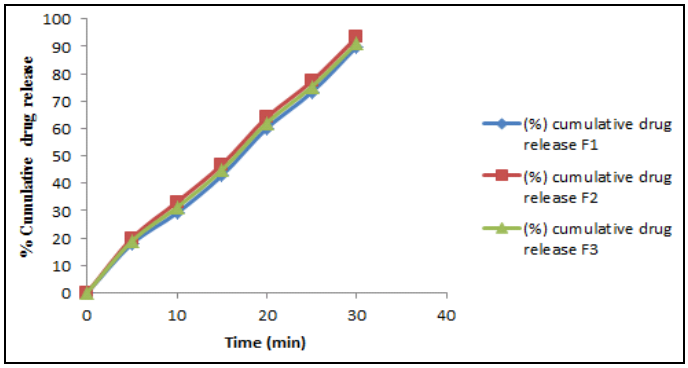


FIG. 20: % DRUG RELEASE FROM F4-F6 BATCHES

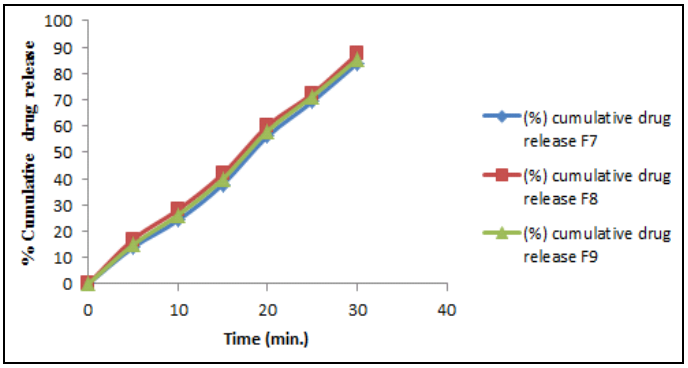
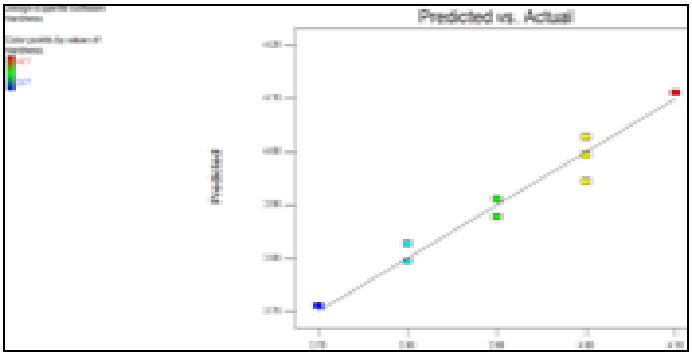
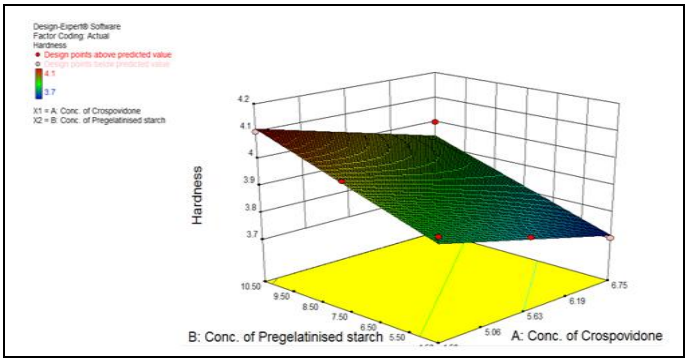


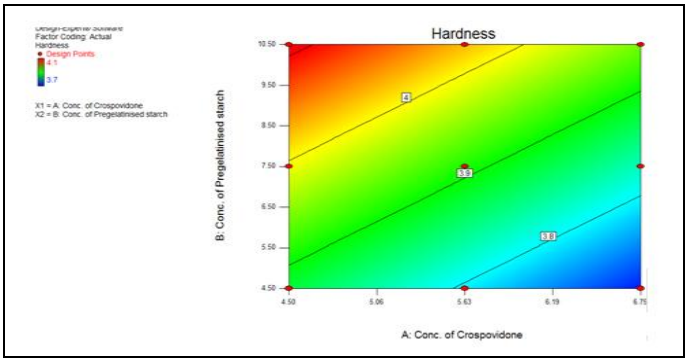
FIG 21: % DRUG RELEASE FROM F7-F9 BATCHES



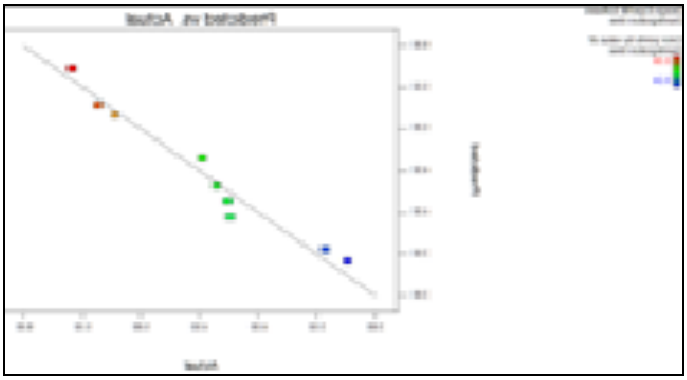
PREDICTED V/S ACTUAL PLOT FOR HARDNESS (Y1)



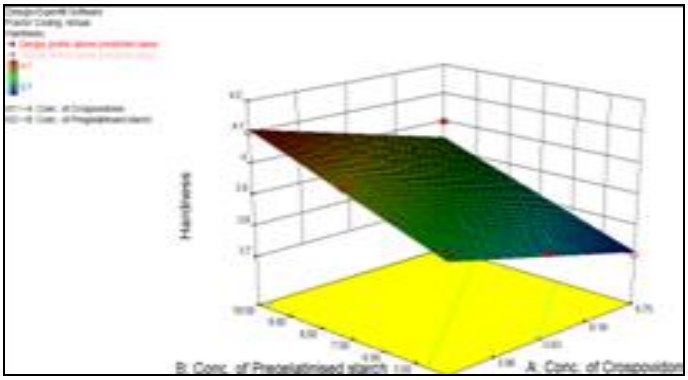
3-D RESPONSE CURVE FOR HARDNESS (Y1)



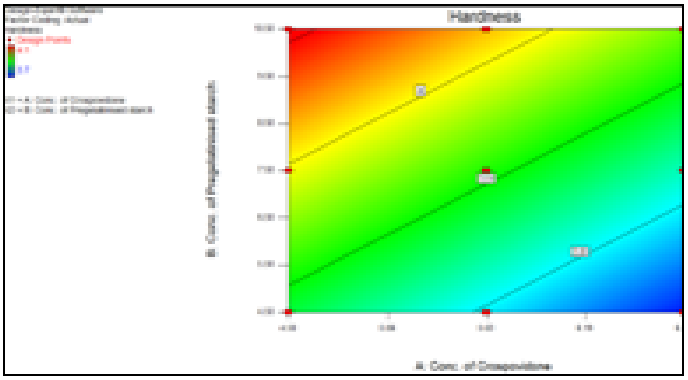
COUNTER PLOT FOR HARDNESS (Y1)



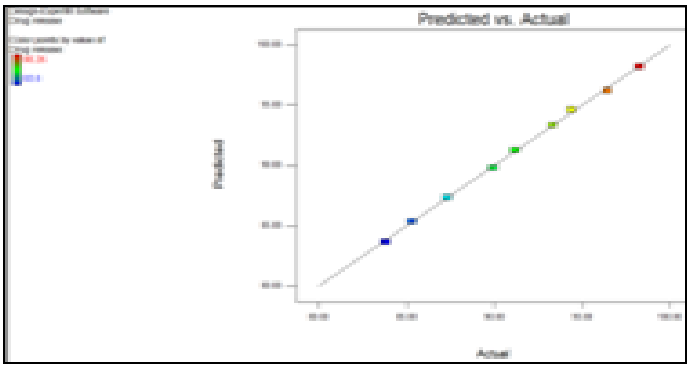
PREDICTED V/S ACTUAL PLOT FOR DISINTEGRATION (Y2)



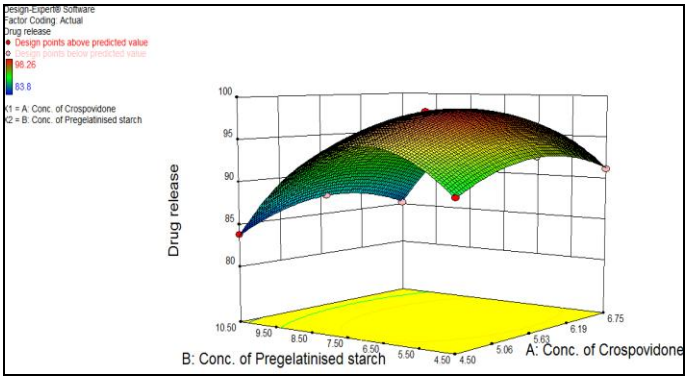
3-D RESPONSE CURVE FOR DISINTEGRATION (Y2)



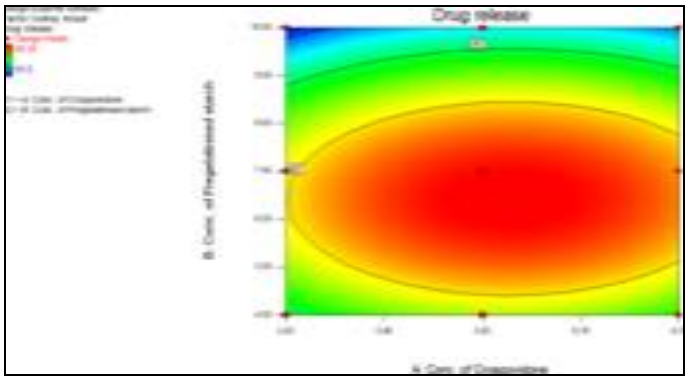
COUNTER PLOT FOR DISINTEGRATION (Y2)



PREDICTED V/S ACTUAL PLOT FOR DRUG RELEASE (Y3)



3-D RESPONSE CURVE FOR DRUG RELEASE (Y3)



COUNTER PLOT FOR DRUG RELEASE (Y3)

B. For Dependent Variable for Disintegration (Y2):

Final Equationin Terms of Coded Factors: Disintegration time = + 3.41-0.19 * A+0.51 * B-0.025 * A * B+0.34 * A2+1.24 * B2.

Final Equation in Terms of Actual Factors: Disintegration time = + 19.00278 - 3.12222 * Conc. of Cros povidone -1.85944 * Conc. of Pregelatinised starch-7.40741E-003 * Conc. of Cros povidone * Conc. of Pre gelatinised starch +

0.26733 * Conc. of Cros povidone 2 + 0.13815 * Conc. of Pregelatinised starch [2.]

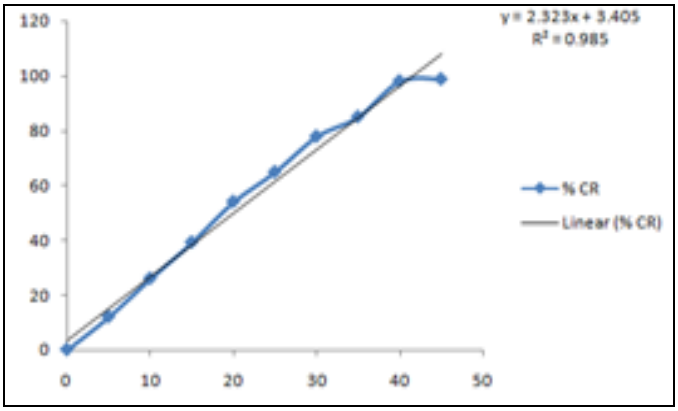
C. For Dependent Variable for Drug Release (Y3):

Final Equationin Terms of Coded Factors: Drug release =+98.22+0.79 * A-3.00 * B+0.060 * A * B-2.80 * A2-7.88 * B2

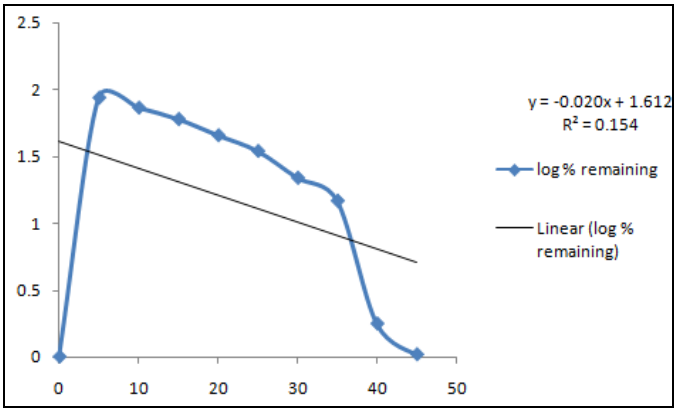
Final Equation in Terms of Actual Factors: Drug release = -16.78014+25.47407 * Conc. of Crospovidone +12.03444 * Conc. of Pregelatinised starch + 0.017778 * Conc. of Crospovidone * Conc. of Pregelatinised starch-2.21366 * Conc. of Crospovidone 2-0.87574 * Conc. of Pregelatinised starch [2].

From the results of 3^2 factorial designs, it was found that as superdisintegrant concentration increases, hardness decreases.

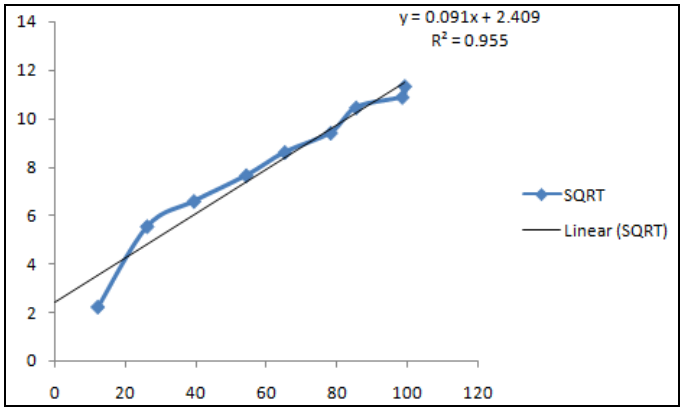
Also, these results show that as superdisintegrant concentration increases, it shows a decrease in disintegration time (sec) at some level, and then it increases.



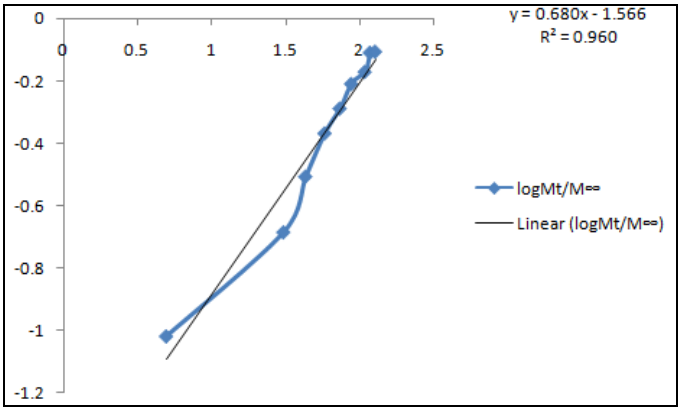
ZERO ORDER KINETIC PLOT



FIRST ORDER KINETIC PLOT



HIGUCHI MODEL PLOT



KORSMEYERPEPPAS PLOT

FIG. 22: KINETIC TREATMENT OF DISSOLUTION DATA

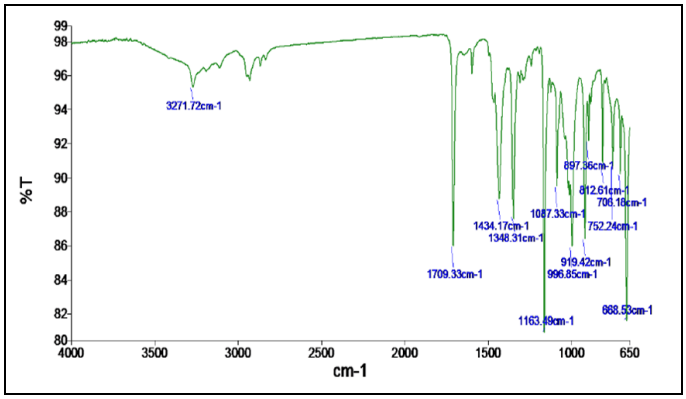


FIG. 23: FT-IR SPECTRA OF OPTIMIZED BATCH OF TABLET

Also, as superdisintegrant concentration increases, percent drug release increases to some extent and then decreases. Effect of binder concentration on hardness shows that, as binder concentration increases, hardness and disintegration time increases. Results show that, as binder concentration increases, percent drug release decreases.

TABLE 11: ACCELERATED STABILITY STUDY OF OPTIMIZED FORMULATION

Time (Months)	Drug content (%)	*In-vitro* drug release (%)
0	99.65±1.40	98.269±0.187
1	98.17± 0.4283	97.898±0.086
2	97. 67±0.42	98.145±0.074
3	98.17±1.544	98.318±0.214
6	98.41±0.8566	98.244±0.154

TABLE 12: LONG TERM STABILITY STUDY OF OPTIMIZED FORMULA

Time (Months)	Drug content (%)	*In-vitro* drug release (%)
0	99.65±1.40	98.269±0.187
3	98.17±1.544	98.541±0.043
6	97.41±0.856	97.368±0.074
9	98.78±1.483	98.665±0.074
12	98.24±2.674	97.972±0.043

Stability Studies: Stability data revealed no significant change, and all are within acceptable limits as shown in **Tables 11** & **12**.

CONCLUSION: The nanosponges were formulated which aimed to achieve improved solubility of Gliclazidea second generation sulphonylurea, used in the treatment of type 2 diabetes mellitus.

It is BCS class II drug having low bioavailability due to extensive first-pass hepatic metabolism, and binding to plasma protein (94%) reduces its aqueous solubility. Nanosponge preparation is an attractive concept in that the drug can be entrapped inside the polymer. SEM image shows that the drug may be present in the bulk of the nanosponges and not surface associated. TEM photographs showed that nanosponges were spherical in shape. *In-vitro* drug release studies revealed that the concentration of polymer in the nanosponges, the volume of cross-linking agent, and emulsion stabilizer concentration affect the *in-vitro* drug release. G5 batch was selected as an optimized batch. Immediate release tablet containing 3.75% concentration of crospovidone and 5% conc. of pregelatinized starch had shown good potential results.

ACKNOWLEDGEMENT: Authors are thankful to Wockhardt Pharmaceutical Ltd., Aurangabad. For providing a gift sample of Gliclazide.

CONFLICTS OF INTEREST: There is no conflict of interest.

REFERENCES:

1. Resztak M, Hermann TW, Sawicki W and Danielak DZ: Pharmacokinetics and pharmacodynamics of gliclazide from immediate and modified release formulation tablets in rats. Iran J of Pharma Research 2014; 13(1): 29-37.
2. Timothy ME, Davis, Frank D and John P: Pharmaco-kinetics and pharmacodynamics of Gliclazide in Caucasians and Australian Aborigines with type 2 diabetes. Br J Clin Pharmacol 2000; 49(3): 223-30.
3. Gedam SS and Basarkar GD: Nanosponges: An attractive strategy for enhanced therapeutic profile. J Pharm Sci & Res 2019; 11(6): 2479-87.
4. Indian Pharmacopoeia: Govt. of India, Ministry of Health & Family welfare, published by the Indian Pharmacopoeia Commission, Gaziabad, 2010; 2: 1417-18.
5. Hiremath SN, Raghavendra RK, Sunil F and Danki LS: Dissolution enhancement of Gliclazide by preparation of inclusion complexes with β-cyclodextrin. Asian Journal of Pharmaceutics 2014; 01: 73-76.
6. Lakka NS and Goswami N: Solubility and Dissolution profile studies of gliclazide in pharmaceutical formulations by RP-HPLC. Int Res J Ph 2012; 3(6): 126-29.
7. Bolmal UB, Manvi FV and Rajkumar K: Recent Advances in Nanosponges as Drug Delivery System. International J of Pharma Sci and Nanotechnology 2013; 6(1): 1934-44.
8. Gedam SS, Jadhav P, Talele SG and Jadhav A: Effect of cross-linking agent on development of gastroretentive mucoadhesive microspheres of risedronate sodium. International J of App Pharmaceutics 2018; 10(4): 134-40.
9. Antonio Z, Antunes T, Saini G and Macgregor A: Factorial design used in optimization immediate release solid dosage ranitidine hydrochloric. Estud Biol 2006; 28: 17-25.
10. Gedam SS and Tapar KK: Formulation and evaluation of mucoadhesive microspheres for nasal drug delivery. Am J Pharm Tech Res 2015; 5(5): 1-22.

11. Jadhav SB, Mali Rajeghadage SH and Bathe RS: Formulation and evaluation of immediate release tablets of Imipramine hydrochloride. International Journal of Biomedical and Advance Research 2014; 05(11): 559- 65.
12. Vamshi Priya V, Rao GC, Reddy DS and Reddy VP: The Effect of different superdisintegrants and their concentrations on the dissolution of topiramate. Immediate Release Tablets 2009; 2(2): 531-36.
13. Atram SC: Formulation and evaluation of immediate release tablet using response surface methodology. Asian Journal of Pharmaceutics 2011; 46-51.
14. Pande V, Karale P, Goje P and Mahanavar S: An Overview on Emerging Trends in Immediate Release Tablet Technologies. Austin Therapeutics 2016; 3(1): 1-8.
15. Remya PN, Saraswathi TS, Sangeetha S and Damodharan NK: Formulation and Evaluation of Immediate Release Tablets of Acyclovir. Journal of Pharmaceutical Sciences and Research 2016; 8(11): 1258-61.
16. Alburyhi M, Alwan M and Aboghanem A: Effect of different excipients on formulation of immediate-release Artemether/Lumefantrine tablets. Journal of Chem and Pharma Res 2013; 5(11): 617-25.
17. Chime SA, Brown S and Ugwu: Effect of binder type and concentrationon the *in-vitro* properties of *Alstonia boonei* tablets. Int J Pharm Sci Rev Res 2012; 2(2): 5-9.
18. Sharma Nand TD: Determination of the concentration blends of superdisintegrant for fast disintegrating tablets. Inte J of Pharma Sci and Research 2011; 2(11): 2828-35.

How to cite this article:
Gedam SS and Basarkar GD: Development, optimization and *in-vitro* characterization of gliclazide nanosponge tablets for oral administration. Int J Pharm Sci & Res 2021; 12(4): 2158-74. doi: 10.13040/IJPSR.0975-8232.12(4).2158-74.