ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Formulation and evaluation of guar gum based matrix tableted glibenclamide microspheres

Prashant Singh*[1], Ritu M. Gilhotra[2]

[1]Research Scholar, Suresh Gyan Vihar University, Jaipur, Rajasthan, India
[2]Faculty of Pharmacy, Suresh Gyan Vihar University, Jaipur, Rajasthan, India

Article History:

Received on: 10 Mar 2020
Revised on: 14 Apr 2020
Accepted on: 29 Apr 2020

Keywords:

Tableted microspheres, matrix tablet, guar gum, hypoglycemic, in-vitro evaluation

ABSTRACT

The purpose of this investigation is to establish anti-diabetic activity relationship as well as efficiency of formulated guar gum matrix tablet using microencapsulated glibenclamide (GBLD). This research is an approach to utilize pharmaceutical excipients as an alternative hypoglycemic agent. In order to execute the objective, GBLD microspheres were formulated by emulsion solvent evaporation method using dichloromethane and methanol as solvent system which was transferred drop after drop into encapsulating medium i.e. liquid paraffin light. The formulated microspheres were exposed to various assessment parameters like drug entrapment efficiency, % yield, particle size distribution, and average particle size, the morphology of surface, dissolution study (in vitro) and micromeritics of prepared microspheres. By using these microspheres, matrix tablets were then prepared which were further evaluated for weight variation, thickness, friability, hardness, drug content, stability study, disintegration time, swelling index and dissolution (in vitro) studies were carefully carried out. Betwixt all the formulated microspheres GEM3 was found to best optimized with respect to evaluation parameters. The results obtained were found within the desired ranges where % yield 93.75%, drug entrapment efficiency 95.627% at 12^{th} hour, and the average particle size was observed to be 179.4$\pm$0.12 μm. Then, by using the method of direct compression matrix tablets of optimized microspheres GEM3 were prepared and drug release (in vitro) was performed. The obtained results of performed parameters on matrix tableted microspheres were within the acceptable range according to IP guidelines. Out of all formulated matrix tableted microspheres, formulation GMT4 and GMT7 showed an in-vitro % drug release of 95.257 and 94.404 at 12^{th} hour in pH 7.4 phosphate buffer.

*Corresponding Author

Name: Prashant Singh
Phone: +91-8948598160
Email: prashantsingh30785@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2238

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INTRODUCTION

Betwixt all the routes of drug administration, dosing of drug through oral route has been the oldest and established as safest and the most convenient route of drug administration. When we consider dosage forms administered orally, solid oral dosage forms are more reliable among them. The advantages of formulations included in the solid orals, because of which it can be categories superior then the other routes can be concluded as no pain while administration, no skilled person or device is required for administration, most stable and cost

effective and compliance of the patient is comparatively high. (Pinjari *et al.*, 2017; Singh *et al.*, 2015).

The matrix tablet is betwixt the most effective and simplest solid dosage forms. The physicochemical nature of the matrix tablet controls the drug release rate, as well as the compression technique, sustained its drug release rate. The matrix system has been confirmed as the most promising among all the oral formulations for controlled and sustained release because of its simplicity, easy formulation methodology, high reproducibility, and drug stability (Sahadevan *et al.*, 2012; Al-Saidan *et al.*, 2005).

The dispersion of solid drug particles within a hydrophilic or hydrophobic polymeric porous matrix tablet system. The drug release from the matrix tablet relies upon the structure and properties of the polymers used. Natural gums are more preferably used in the formulation as they are not toxic and inert. Guar gum (GG) is a natural, high molecular weight polymeric structured with a lot of hydroxyl groups. GG is a hydrophilic and potential adjuvant for swellable controlled drug delivery frameworks. Therapeutically, GG has been utilized as a part of the diet of patients with diabetes mellitus. Several in-vivo hypoglycemic activities of GG have been previously reported (Saeed *et al.*, 2012a; Singh *et al.*, 2011).

Microspheres are 1 to 1000 μm sized, spherical, multi-particulate drug carrier systems, which boost the bioavailability in demonstrate hatred for that the medication experiences broad first-pass digestion. Such system provides constant and prolonged therapeutic effect and target drug to specific sites with minimizing side effects (Parida *et al.*, 2016a).

Not with standing the fact that in the number of polymers, Ethylcellulose (EC) is chosen. It is a polymer of ß-hydro-glucose building squares consolidated by acetal holding and considered as a non-poisonous, biocompatible, non-biodegradable and water-insoluble polymer. EC based microencapsulated drug conveyance frameworks are by and large widely studied for accomplishing broadened drug discharge and shielding the core substance from deterioration., also in-vitro drug rdischarge conduct dependent on the characteristics of linkage between drug and EC. (Murtaza, 2012; Srivastava *et al.*, 2013).

GBLD is certified by FDA as type 2 diabetes second-generation sulfonylurea drugs, for clinical use of oral non-insulin dependent diabetes mellitus. The medication in oral traditional measurement structure has the dosing system of ter-in-pass on due to having short disposal $\frac{1}{2}$ life of 5 hours. (Rani *et al.*, 2014) An anti-diabetic, interdependent investigation was performed using GBLD loaded ethyl cellulose microspheres based guar gum matrix tablet (Toti and Aminabhavi, 2004).

MATERIALS AND METHODS

Materials required in this investigation are as follows,

1. GBLD- Gift sample from Prudence Pharma Chem, (Batch No.:GLB/M020/07/16)
2. Ethyl cellulose- Loba Chemie Pvt. Ltd., Mumbai.
3. Guar gum, MCC, Tween 80, Dichloromethane and Methanol– Merck/ Merck Specialities/ Merck Life Science Pvt. Ltd., Mumbai

Method

Formation of microspheres

The preparation of microspheres were carried out by the method called emulsification solvent evaporation. Accurately measured dichloromethane and methanol in the ratio of 1:1 were taken and various drug: polymer ratios were added. Total 4 formulations i.e. GEM1, GEM2, GEM3, and GEM4 were prepared with the This above solution was dispersed dropwise in a separate 250 ml beaker containing 100 ml of distilled water and 0.5ml of tween 80 which was preheated to 37ºC. This temperature was maintained during stirring resulted in maximum evaporation of the dispersed liquid which was set aside to cool after 45 minutes. The cooling for the remaining 15 minutes provides the hardening of spherically formed microspheres. The stirring speed was 1000 rpm and stirring was carried out for (45+15) 60 minutes. Then later obtained microspheres were washed with distilled water and dried (Rai and Ravikumar, 2016).

Evaluation of Microspheres

Frequency distribution analysis (Particle Size Analysis)

Assurance of particle size (average) of GBLD microspheres was carried out by optical microscopy employed which stage micrometer. A minute quantity of GBLD microspheres was spread on a clean glass slide and average size of 300 GBLD microspheres was determined in each batch. So as to have the option to characterize a size distribution or contrast the characteristics of particles with many different diameters, the size distribution can be broken into different size ranges, which can be presented as a histogram. The histogram presents an understanding of the particles size dispersion and empowers the level of particles having a given equivalent diameter to be determined (Rama *et al.*, 2005).

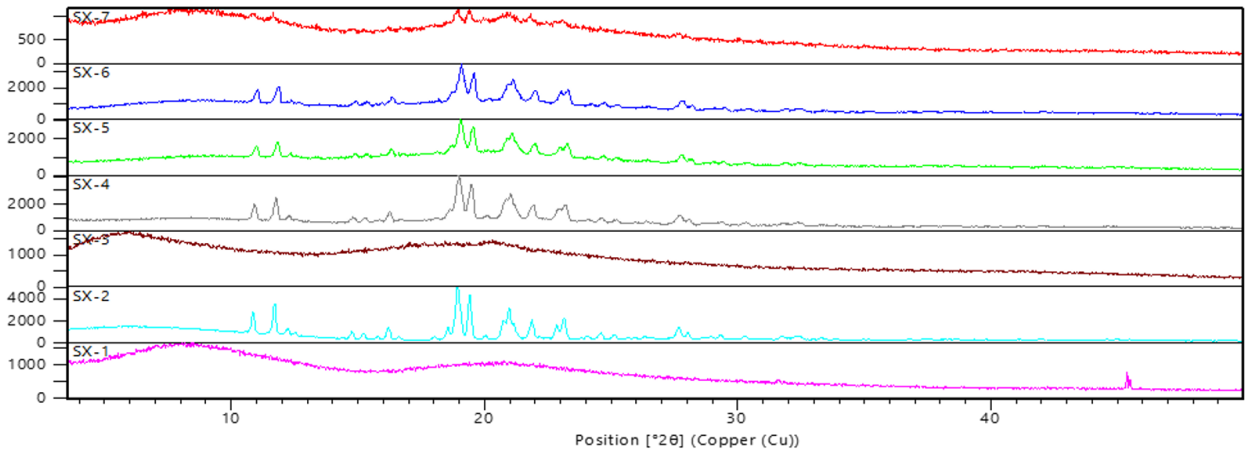

Figure 1: Combined XRD data for EC (SX-1), GBLD (SX-2), GG(SX-3), Physical Mixture of EC & GBLD (SX-4), Physical Mixture of EC, GG& GBLD (SX-5), Matrix Tablet of EC, GG & GBLD (SX-6), and GBLD loaded

Table 1: Characteristic IR absorption peaks of: (A) GBLD puredrug; (B) Physical Mixture of GBLD+ EC+ GG; (C) Microspheres; (D) Matrix Tablet

Wave number of GBLD	Wave number (cm^{-1})		
	Physical mixture "B"	Microspheres "C"	Matrix Tablet "D"
3119.7 (N-H stretching)	3123.9	3118.7	3119.9
2932.1 (Aliphatic C-H stretching)	2930.6	2930.9	2929.3
2856.0 (O-H stretching)	2856.5	2855.8	2866.6
1527.6 (N=O stretching)	1528.5	1524.8	1528.6
1158.4 (C-N stretching)	1157.1	1159.0	1157.1

Table 2: Frequency distribution data of GBLD loaded EC microspheres

	Size range (μm)	Formulation Code			
		GEM1	GEM2	GEM3	GEM4
Frequency	0-30	35	30		
	30-60	60	38		
	60-90	85	50	14	
	90-120	65	69	27	28
	120-150	40	46	63	61
	150-180	15	35	75	78
	180-210		21	64	57
	210-240		11	43	37
	240-270			10	29
	270-300			4	7
	300-330				3

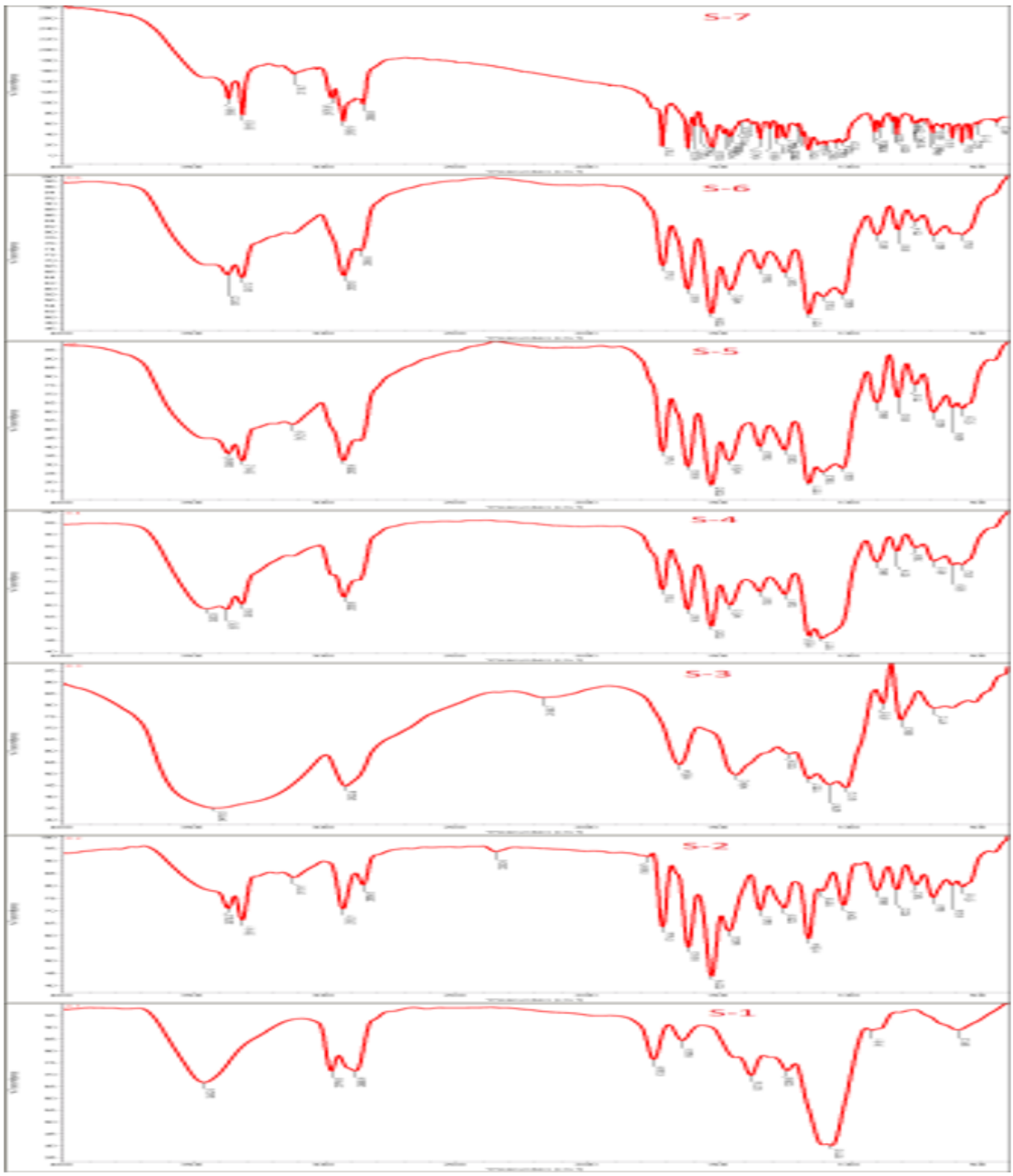

Figure 2: FTIR of data for EC (S-1), GBLD (S-2), GG (S-3),Physical Mixture of EC & GBLD (S-4), Physical Mixture of EC, GG & GBLD(S-5), Matrix Tablet of EC, GG & GBLD (SX-6), and GBLD loaded EC Microspheres (S-7)

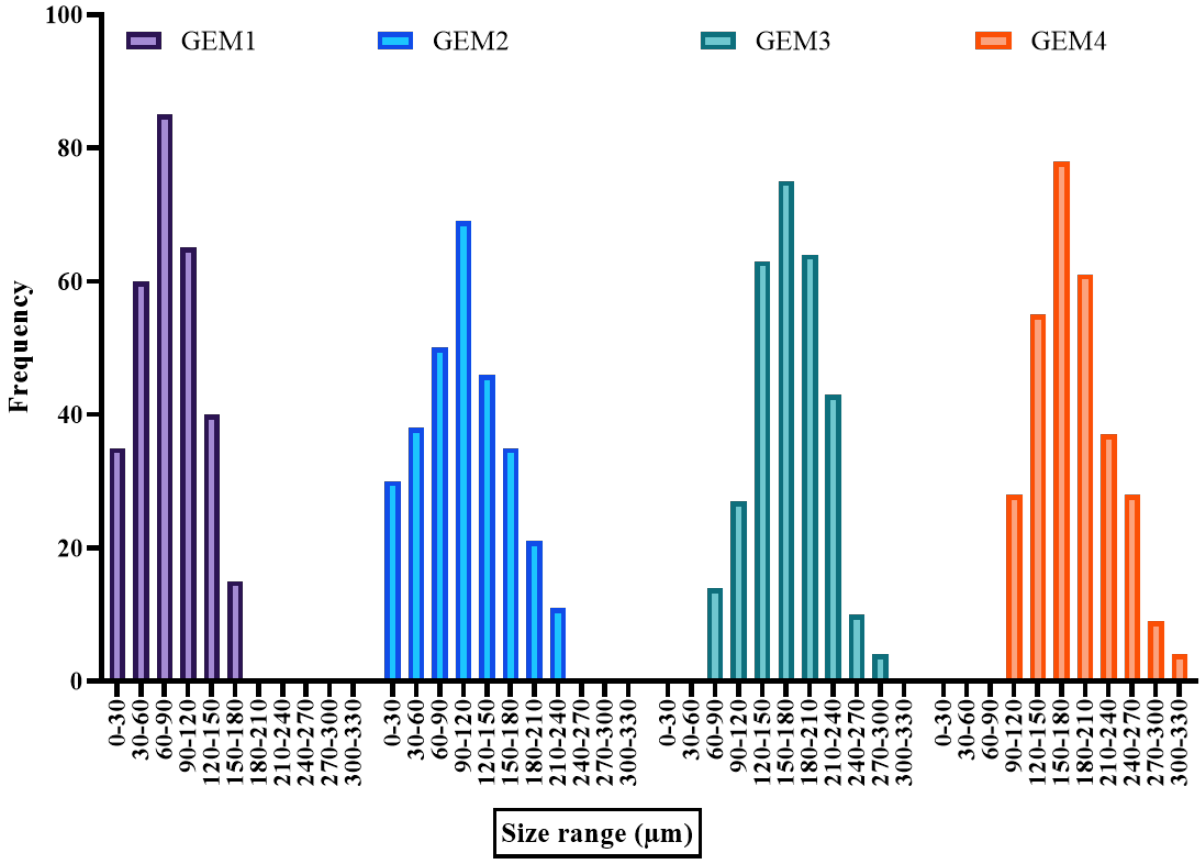

Figure 3: Frequency distribution data of GBLD loaded EC microspheres

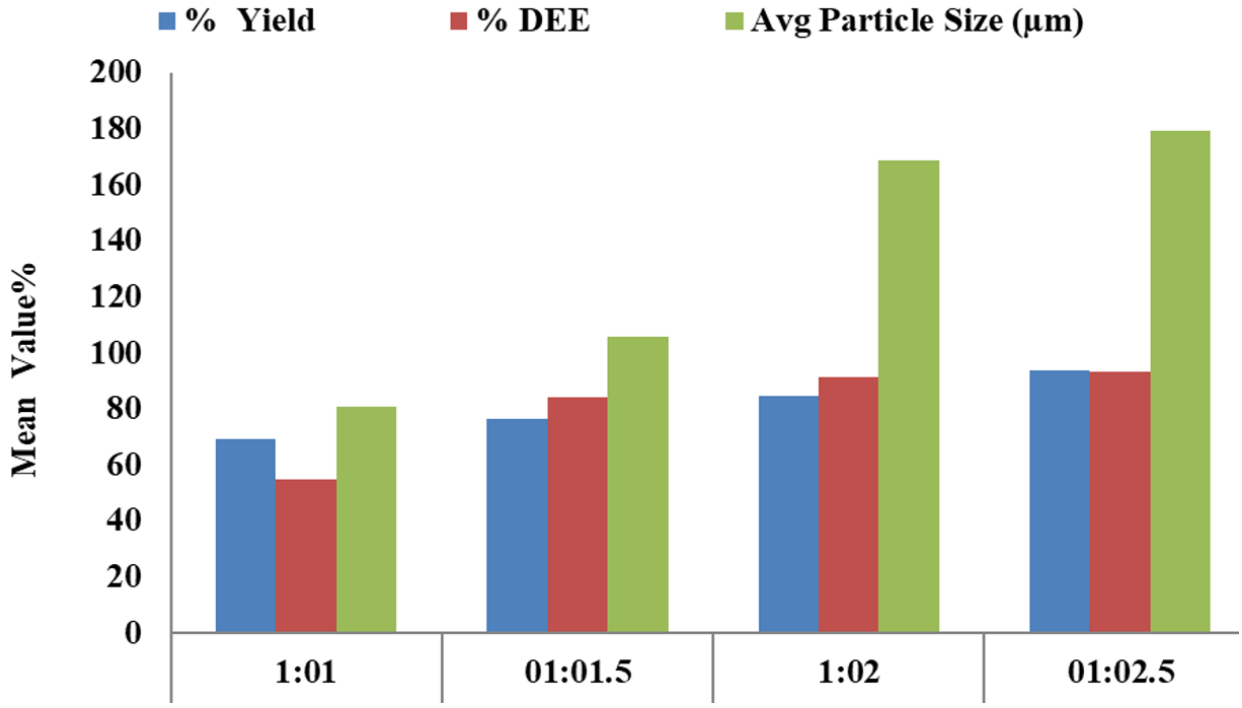

Figure 4: Frequency distribution data of GBLD loaded EC microspheres

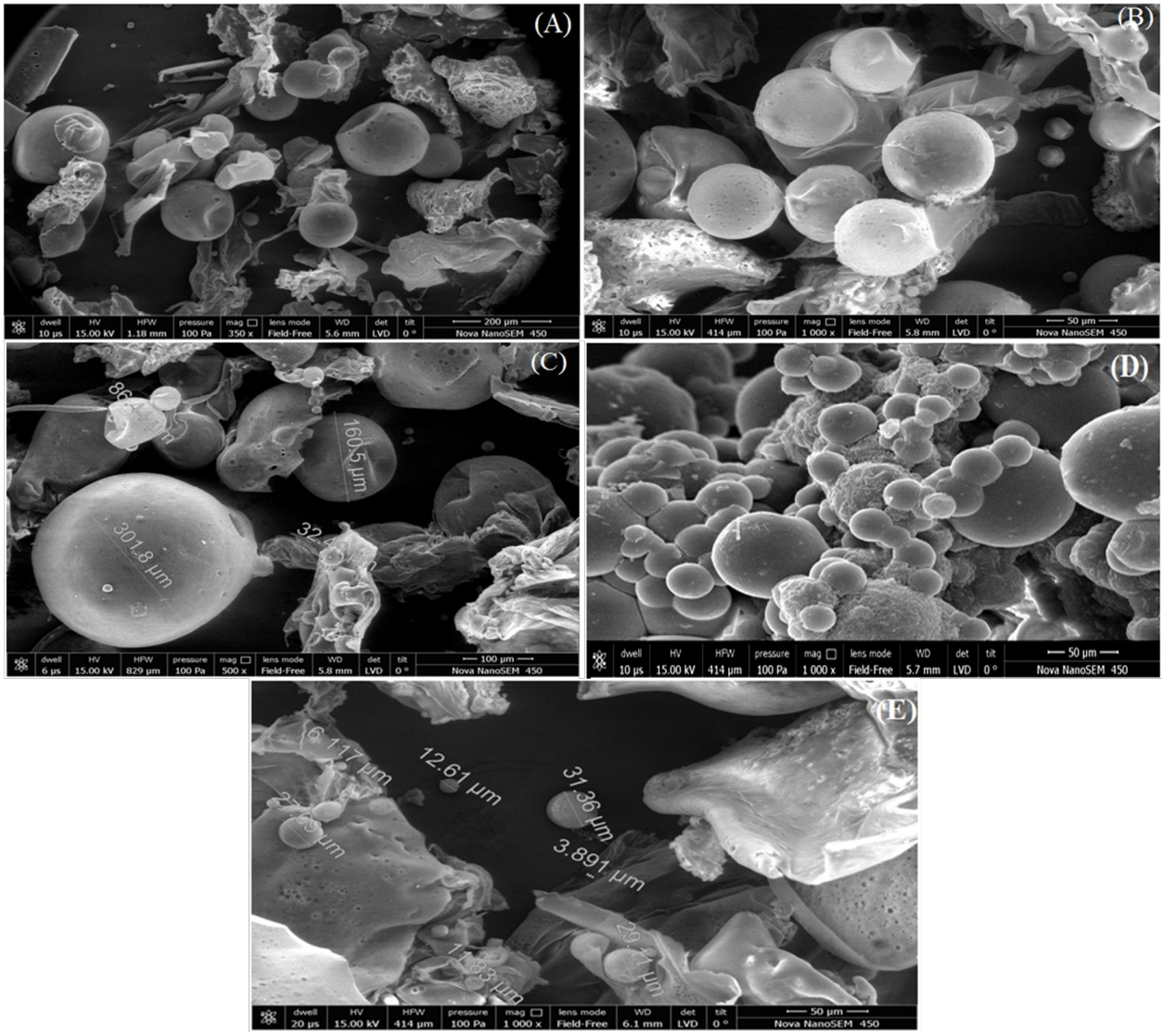

Figure 5: Scanning electron microscopy of GBLD loaded EC microspheres of: (A) GEM1; (B) GEM2; (C) GEM3, (D) GEM4, and (E) Matrix Table

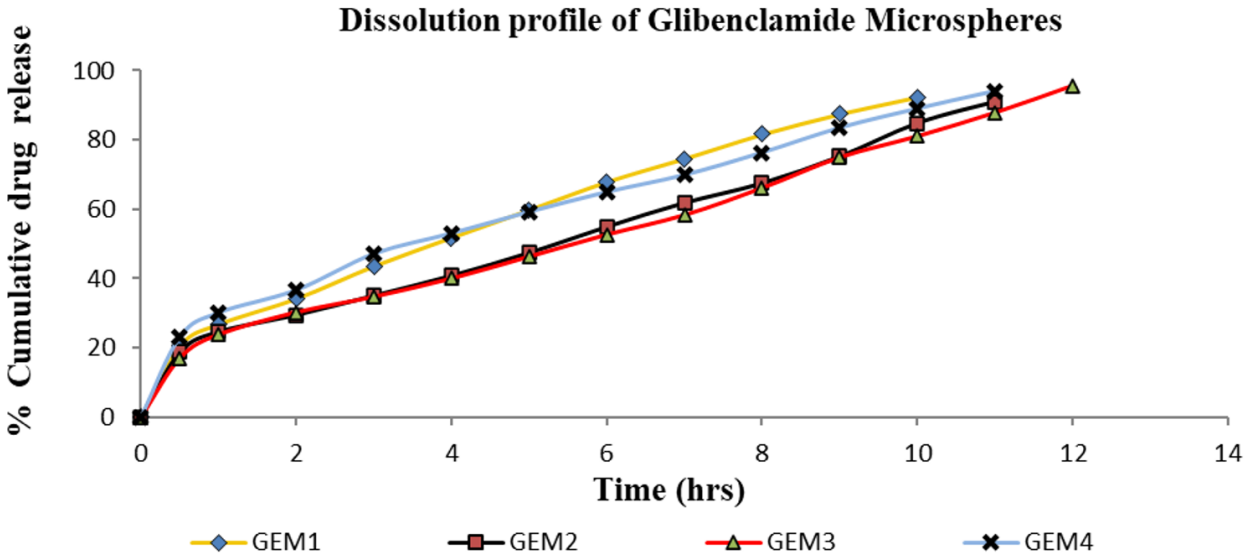

Figure 6: *In-vito* dissolution profile of various formulations of GBLD microspheres

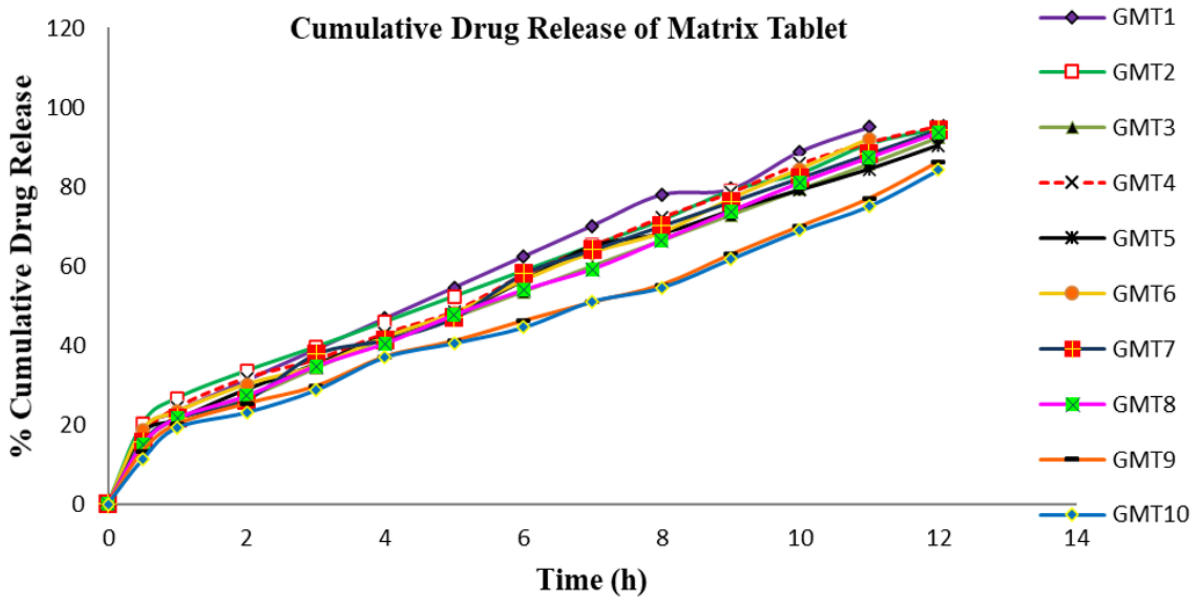

Figure 7: *In-vitro* dissolution profile of various formulations of matrix tablets

Table 3: Effect of drug: polymer ratio, % Yield, % DEE, Average particle size, angle of repose, carr's index and tapped density of GBLD loaded EC microspheres

Formulation Code	Process Variable (Drug: Polymer)	% Yield	% DEE	Average Particle Size (μm)	Angle of Repose (θ)	Carr's Index %	Tapped Density (g/cm^3)
GEM1	1:1	69.21	54.67	81±1.31	26.22±1.1	14.89±0.43	0.8823±0.04
GEM2	1:1.5	76.52	84.39	105.7±1.72	28.37±0.9	14.35±1.21	0.8571±0.01
GEM3	1:2	84.73	91.50	168.7±1.11	28.49±0.5	16.28±0.72	0.8571±0.03
GEM4	1:2.5	93.75	93.38	179.4±0.12	29.27±1.2	14.29±0.65	0.8652±0.05

Table 4: Various frameworks of the model equations of the GBLD microspheres in-vitro release kinetics

Formulation	Zero order	First order	Higuchi	Korsemeyer-Peppas	
				R^2	n
GEM1	0.9646	0.9575	0.9901	0.9850	0.5210
GEM2	0.9773	0.9017	0.9613	0.9539	0.5116
GEM3	0.9809	0.9989	0.9600	0.9636	0.5347
GEM4	0.9464	0.9327	0.9932	0.9862	0.4576

Percentage (%) Yield

Deciding if the readiness strategy picked for consolidating a medication into the polymers is effective and is of prime significance. The crude materials, the measure of active compound, polymer(s) and different procedure parameters are central elements for the yield of the item during the preparation of microspheres (Asif *et al.*, 2014).

The yield was dictated by gauging the microspheres and afterward discovering the % yield as for the heaviness of the input materials, i.e., weight of drug and polymers used. The formula for calculation of % yield is as follows;

The % yield of prepared GBLD microspheres was determined by using the formula,

$$\%\ yield\ = \frac{weight\ of\ microparticles}{Weight\ of\ drug + Weight\ of\ polymers} \times 100$$

Determination of drug incorporation efficiency

Drug loading (DL) and Drug Entrapment Efficiency (DEE)

Table 5: Characterization of prepared matrix tableted microspheres

Formulation	Evaluation Parameters					
	Weight Variation (g)	Thickness (mm)	Hardness Kg/cm^2	Friability (%)	Disintegration Time (min)	Drug Content (%)
GMT1	275.9±0.67	3.37±0.02	3.86±0.11	0.77	18.5±1.5	97.4
GMT2	325.55±0.88	3.43±0.021	4.81±0.01	0.721	19.75±0.69	96.2
GMT3	375.75±1.831	4.28±0.041	4.89±0.66	0.625	20±2.16	99.9
GMT4	425.05±0.887	4.79±0.071	5.72±0.03	0.882	21.25±1.46	99.1
GMT5	475.4±0.754	4.61±0.046	5.89±0.07	0.757	34.33±1.70	95.7
GMT6	250.6±0.940	2.78±0.012	4.05±0.01	0.837	15.5±0.96	100.1
GMT7	300.3±1.174	4.65±0.01	5.80±0.1	0.899	18±0.82	97.3
GMT8	350.05±0.605	4.26±0.01	4.91±0.01	0.728	23.33±1.25	96.7
GMT9	400.35±1.785	4.30±0.042	5.06±0.02	0.861	31.83±2.16	98.0
GMT10	450.6±1.535	4.53±0.041	5.12±0.03	0.734	58.16±1.55	99.6

Table 6: Various frameworks of the model equations of the matrix tableted microspheres release kinetics (in-vitro)

Formulation Code	Zero order	First Order	Higuichi	Peppas	
				R2	n
GMT1	0.9750	0.9985	0.9820	0.9793	0.5466
GMT2	0.9646	0.9575	0.9901	0.9850	0.5210
GMT3	0.9843	0.9178	0.9745	0.9828	0.5758
GMT4	0.9791	0.9092	0.9752	0.9773	0.5487
GMT5	0.9757	0.9543	0.9819	0.9762	0.5406
GMT6	0.9793	0.9022	0.9660	0.9599	0.5219
GMT7	0.9822	0.9192	0.9756	0.9796	0.5831
GMT8	0.9854	0.9014	0.9703	0.9805	0.5773
GMT9	0.9798	0.9081	0.9563	0.9730	0.5602
GMT10	0.9827	0.9264	0.9599	0.9794	0.5988

Table 7: Tablet properties of the developed GMT4 tablets during stability studies.

Parameter	Initial	1st Month		2nd Month		3rd Month	
		Control	Accelerated	Control	Accelerated	Control	Accelerated
Thickness (mm)	4.79±0.07	4.76±0.09	4.76±0.08	4.79±0.05	4.69±0.04	4.79±0.02	4.75±0.03
Hardness (Kg/cm^3)	5.72±0.03	5.70±0.04	5.69±0.05	5.70±0.06	5.68±0.07	5.73±0.08	5.57±0.09
Friability (%)	0.882	0.883	0.862	0.872	0.851	0.873	0.861
Drug content (%)	99.1	99.1	98.31	98.33	97.16	97.89	96.15
F2 value (Similarity factor)	-	95.158	94.693	94.76	87.8690	90.57	83.940

Table 8: Tablet properties of the developed GMT7 tablets during stability studies

Parameter	Initial	1st Month		2nd Month		3rd Month	
		Control	Accelerated	Control	Accelerated	Control	Accelerated
Thickness (mm)	4.65±0.01	4.65±0.02	4.61±0.03	4.64±0.05	4.64±0.05	4.65±0.06	4.63±0.07
Hardness (Kg/cm^3)	5.80±0.1	5.80±0.2	5.79±0.3	5.80±0.4	5.78±0.3	5.78±0.5	5.79±0.6
Friability (%)	0.899	0.899	0.896	0.897	0.879	0.898	0.889
Drug content (%)	97.3	97.3	96.774	96.594	96.53	96.673	96.579
F2 value (Similarity factor)	-	95.793	93.741	94.287	90.7840	91.473	86.668

The prepared microspheres (10g) were dissolved in fifty milliliters of dichloromethane (a co-solvent for drug and polymer). The quantity of drug available in the solution was determined by using ultraviolet spectrophotometer at 229 nm. The 2 quations i.e. drug content (in % w/w) and % drug entrapment was calculated. The drug loading and incorporation efficiency (%) were calculated using equations (2) and (3), respectively (Belgamwar *et al.*, 2011).

$$Drug\ loading\ (\%) = \frac{Actual\ drug\ content}{Weight\ quantity\ of\ powder\ of\ microsphere} \times 100$$

$$DEE = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

Flow properties of prepared microspheres

Kotagale *et al.* (2013)The flow properties of the formulated microspheres were classified by performing several parameters which are as follows:

Bulk & Tapped Density

An exact weighted amount of pure medicament and medicament loaded microspheres were taken independently in a 10 ml graduated cylinder. Then, the underlying volume was noted. The graduated chamber was tapped multiple times and the last volume was estimated. The bulk and tapped density were determined from the given formula,

Bulk Density = W_M / V_B,

Tapped Density = W_M / V_T

Where, W_M = Weight of the formulated microspheres, V_B = Bulk Volume, V_T = Tapped Volume.

Carr's Index or Compressibility Index

Carr's Index forecast the preparation which can be resolved as,

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} \times 100$$

Packing Factor / Hausner's Ratio

It is a measure of flow properties, which was calculated as the density ratio of tapped to bulk.

$$Hausner's\ Ratio = Tapped\ Density / Bulk\ Density$$

Scanning electron microscopy (SEM) analysis of microspheres

The microspheres were classified further utilizing a scanning electron microscope (JEOL - JSM-6490, Japan Electron Optics Ltd., Japan). Shapes and surface qualities of the microspheres were explored and photographed (Venkateswarlu, 2017).

XRD analysis of microspheres

XRD analysis provides the information of the crystalline or amorphous nature of the incorporated drug in the developed microspheres. The X-ray generator was operated at 40 mA and 45 kV using the Cu as Anode Material at 1.54060 Å as the radiation source. The samples were ground in a mortar. The triturated specimen was filled and arranged in a specimen holder made of aluminum. The Start Position [°2θ] for the sample was 3.5174 and the End Position [°2θ] was 49.9784 and minimum step size 2θ: 0.001 with Scan Step Time of 29.8450 s. The scannings of samples were done at 25°C (Parida *et al.*, 2016b).

FTIR studies

The physicochemical compatibility of GBLD, physical mixture of GBLD and polymer, GBLD microspheres, physical mixture of tablet ingredients along with gilbenclamide microspheres were studied by using Fourier Transform Infra-Red Spectrometer (FTIR) of Thermo Scientific (Nicolet 6700 FT-IR) Nicolet 6700 FT-IR Spectrometer from Thermo Scientific. The pellets of these examples and potassium bromide were set up by packing the powders at 20

psi for 10 min on KBr-press and the spectra were examined in the wave number range of 4000-400 cm^{-1} (Kashinatha *et al.*, 2012).

In vitro Release Studies

The in-vitro discharge profile of the microspheres was assessed by the USP type II dissolution test device (paddle type) (Lab India 8 crate dissolution mechanical assembly, India) utilizing phosphate buffer (pH 7.4) and set up at 37±0.5°C with the speed of tumult at 100 rpm. The exactly measured amount of microspheres comparable to 10 mg of the medication was set in a jar containing a dissolution medium and the trial was performed. At the prefixed time of interims (0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h), 5 mL of arrangement was pulled back and a similar volume was supplanted with pH 7.4 phosphate support. After reasonable dilution, withdrawn's were measured spectrophotometrically for the medicament content at 229 nm utilizing a UV-Visible spectrophotometer. The active investigations for assurance of in vitro sedate discharge instrument, the acquired medication discharge information were fitted to zero requests, first request, Higuchi's and Korsmeyer-Peppas models (Bhardwaj *et al.*, 2014; Singhavi *et al.*, 2017).

Preparative aspects of Tableted Microspheres

The streamlined GBLD microspheres were directly compressed to shape tablet of 275mg, 325 mg, 375 mg, 425 mg, 745 mg, 250 mg, 300 mg, 350 mg, 400 mg and 450 mg using microcrystalline cellulose as directly compressible diluents as well as disintegrant and guar gum as natural hypoglycemic as well as release retarding agent, magnesium stearate is used as lubricant and talc 2% as glidant. Each tablet contains microspheres containing 10 mg of GBLD and the tablets were coded as GMT1, GMT2, GMT3, GMT4, GMT5, GMT6, GMT7, GMT8, GMT9 and GMT10. Three more tablets without drug were formulated having same guar gum and other additives concentration respectively. These non drug tablets were coded as BMT1, BMT2, and BMT3 (Shivangi *et al.*, 2016; Tomar *et al.*, 2016; A. Gürsoy, 2000).

Physical Characteristics of the Tablets

The physical parameters of matrix tablet like weight variation by digital weighing machine, thickness by vernier calipers, hardness by Monsanto hardness tester and friability by roche's friabilator were performed using 20 tablets for each test.

In-vitro deterioration test was performed utilizing haphazardly chosen 6 tablets in the disintegration test apparatus. The disintegration time was measured in minutes.

The medicament content of the matrix tablet was determined by utilizing 6 separately weighed tablets. These tablets were triturated to powder and powder equivalent to 10 mg of GBLD was taken and dissolved in 100 ml of pH 7.4 phosphate buffer solution. This solution was filtered using Whatmann filter paper (no.41). The drug content was analyzed using UV spectrophotometer at 229 nm (Chang and Robinson, 1990).

In vitro drug release study

In-vitro drug release was conducted on the dissolution assembly USP (Type-II) utilizing 3 tablets from each clump. Every tablet was performed under the sink condition in 900 ml of pH 7.4 phosphate buffer at 37±0.5ºC temperature. The release study was observed for 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 h. At each predetermined time intervals samples were withdrawn and the equal amount was replaced using the same buffer solution.

Accelerated Stability Study

The study was done according to ICH guidelines on optimized tablet. The test was performed for 3 months period. During this period the storage of tablets were maintained at 40ºC temperature and 75% relative humidity. During these three months of storage, tablets were evaluated for visual/ physical inspection for any remarkable changes on tablet surface, assay, hardness, friability and dissolution at every one month intervals. The results of these tests were compared with the control sets. Every month withdrawal of test sample was done and subjected to various tests, including visual inspection for any appreciable change on the tablet surface, assay, hardness, friability, and dissolution (Wagner *et al.*, 2000).

RESULTS AND DISCUSSION

XRD of GBLD and GBLD encapsulated EC microspheres were performed by using an X-ray diffractometer to find out any change in the crystallinity of GBLD during micro encapsulation. XRD pattern of GBLD indicated sharp pinnacles whereas; EC microspheres diminished the sharpness of peak which exhibited that EC scattered the GBLD at subatomic level mixed EC microspheres by diminishing the crystallinity of GBLD (Figure 1). XRD patterns of GBLD and GBLD loaded EC microspheres (Figure 1) showed the adjustment in the crystalline idea of GBLD might be due to the addition of EC polymers and these polymers helped in spreading the GBLD completely at the sub-atomic level. The peaks in SX-4, SX-5, SX-6, and SX-7 similar to SX-2 between 10º to 30º justifies that GBLD is stable

in physical blends, prepared microspheres and in matrix tableted microspheres.

The pinnacles (cm^{-1}) of GBLD (pure drug) by FTIR spectr of N-H stretching, aliphatic C-H stretching, O-H stretching, N=O stretching and C-N stretching assignment were 3119.7, 2932.1, 2856.00, 1527.6 and 1158.4 respectively, whereas observed peaks of drug found in physical mixture, microspheres and matrix tablet are shown in Table 1.

Post-comparing the FTIR spectra of given drug, physical blends of drug-polymers, formulation of drug loaded microspheres and tableted microspheres (Figure 2), it was observed that there were noticeable peaks of several functional groups in the physical blend and preparation which can be recognized in the pure medicament spectra. This uncovered that there was no interaction among medicament and polymers used to formulate microspheres and matrix tablet.

The formulation of microspheres was optimized by changing the polymer ration to the fixed amount of polymer. The stirring speed plays an important role in percentage yield and particle size distribution of microspheres. Above one thousand rpm stirring speed causes breaking of microspheres as well as the evaporation rate affect the % yield and drug content.

Evaluation of microspheres

The frequency distribution of microspheres were measured for all the formulation and the size was observed in the frequency band starting from 0-30 μm and ends upon 300-330 μm (Table 2; Figure 3). The effect of process variable (drug: polymer ratio) on percentage yield of GBLD loaded EC microspheres ranges from 69.21 to 93.75 %, percentage drug entrapment efficiency ranges from 54.67 to 91.50 % and average particle size ranges from 81 to 179.4 μm in diameters (Table 3; Figure 4). The rise in polymer concentration is directly proportional to entrapment efficiency and average particle size (Valizadeh *et al.*, 2010). It has also been observed that, higher the concentration of polymer significantly raises the viscosity which results in forming larger microspheres (Rajan and Raj, 2013).

The SEM study should an increase in microsphere diameter with increase in GLBD/ EC ratio (Table 3). In 2001, similar results were reported by Pérez-Martínez using EC polymer for controlled release microspheres. (Pérez-Martínez *et al.*, 2001) The microspheres were observed round in shape with a smooth surface shown in Figure 5 (A to D) for formulation GEM1, GEM2, GEM3 and GEM4 respectively (Amin *et al.*, 2016).

The flow property of the microspheres was carried out by figuring the angle of repose (θ) and % compressibility index (CI). The acquired information alongside related parameters are introduced in Table 3. The values of θ ranged from 26.22 to 29.27 indicating that the calculated data were well within the criteria. This result clearly shows that the prepared microspheres have good flow potential. The good value of the carr's index was found within the range of 14.29$\pm$0.65 to 16.28$\pm$28%. The values of tapped density ranged between 0.8333$\pm$0.03 to 0.8823$\pm$0.04 g/cm3. The difference in density among the preparations is insignificant and the density values of preparations were well within the desired criteria, demonstrating that the prepared microspheres were non-aggregated (Gaur *et al.*, 2014).

The in-vitro releases of microspheres were carried out in phosphate buffer (pH 7.4) and the % of drug release was calculated. Formulation GEM1 at $\frac{1}{2}$ an hour and 10th hour shows % drug release of 20.423 and 92.387 respectively, formulations GEM2 and GEM4 at $\frac{1}{2}$ an hour shows 18.671 and 23.121 as well as at 11th hour shows 91.026 and 94.118 of % drug release respectively. Formulation GEM3 shows % drug release of 16.989 and 95.637 at $\frac{1}{2}$ an hour and 12^{th} hour respectively. Moreover, the data obtained were fitted to the Korsemeyer-Peppas Model in order to find out 'n' value which portrays the medicament discharge mechanism. The 'n' value of all preparation found between 0.5- 1, indicating the drug release to be non-fickian diffusion-controlled which is shown in Table 4; Figure 6.

Evaluation of Matrix Tablet

The tablet was directly compressed using the most suitable optimized formulation of microspheres. The selection of microspheres was based on the results obtained. The matrix tablet was formulated using 23.53 mg of microspheres which has entrapped 10 mg of GBLD. These tablets were assessed for different parameters such as thickness, hardness, weight variation, friability and in-vitro disintegration time given in Table 5. The microspheres inside the tablet maintained their morphology with no significance alteration in their surface profile Figure 5(E).

So as to consider the mechanism of matrix tableted microspheres, the drug discharge information was fitted to different kinetic models (zero-order, first, Korsmeyer-Peppas, and Higuchi). The modeling outcomes are conferred in Table 6.

To portray the release mechanism, the estimation of n as a discharge exponent in the Korsmeyer-Peppas model was determined. The n value was above 0.5

for all the preparation. This confirms that anomalous diffusion i.e. non-fickian diffusion, which controls the GBLD release from matrix tableted microspheres and follows first order release. The % cumulative drug release (%CDR) of all tablets is shown in Figure 7. The formulations GMT4 and GMT7 were selected based on %CDR of 95.257 and 94.404 respectively. Optimized formulation shows the remarkable sustained release effect under in-vitro studies. The guar gum plays a vital hypoglycemic impact and significantly decreases the glucose absorption from the stomach (Saeed *et al.*, 2012b).

This optimized formulation can be further investigated for the impact of guar gum in combination with GBLD.

The studied outcomes of stability of the chosen batches GMT4 and GMT7 are shown in Tables 7 and 8. The accelerated stability studies reveal that the refined matrix tableted microspheres are unchanged after 3 months storage under elevated conditions as no sign of identical distinguishable changes are observed in the visitation, surface and pigmentation of the preparation. The information on drug substance and friability are equivalent to those of the control tests and are found inside the desired points. F2 estimations of 50–100 demonstrate similitude between the dissolution profiles. Based on these outcomes, it might be reasoned that the streamlined plan created is steady under accelerated conditions for 3 months.

CONCLUSIONS

The after-effects of the current investigation showed that the arrival of guar gum-based matrix tableted GBLD microspheres. The in-vitro dissolution information represents the impact of guar gum concentration on medicament release based on which formulation GMT4 and GMT7 were chosen. These optimized streamlined formulations might be additionally exposed to an in-vivo animal study to establish to build up a hypoglycemic impact of guar gum. This formulation may be developed in order to reduce the drug dose when given in combination with guar gum due to additive or synergistic effect or else the guar gum can be developed as an alternate approach of natural hypoglycemic nutraceuticals.

ACKNOWLEDGEMENT

All support to investigate this research work from Dr. Ravindra Pal Singh, Principal, NIMS Institute of Pharmacy, NIMS University, Jaipur and Dr. D.V. Gauda, HOD, Department of Pharmaceutics, JSS College of Pharmacy, J.S.S University, Mysore is acknowledged. Dr. Santosh Kumar Singh, Principal, College of Pharmacy, Suresh Gyan Vihar University, Jaipur is also acknowledged for his encouragement.

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