Digest Journal of Nanomaterials and Biostructures Vol. 6, No 4, October-December 2011, p. 1463-1477

IMPROVEMENT IN COMPRESSIBILITY, FLOWABILITY AND DRUG RELEASE OF GLIBENCLAMIDE BY SPHERICAL CRYSTALLIZATION WITH ADDITIVES

S. V. PATIL [a,b*], SAHOO S. K.[a]
[a]*Department of Pharmaceutics, University Department of Pharmaceutical Sciences, Utkal University, Bhubaneswar, Orissa. India*
[b]*Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Maharashtra. India*

Spherical agglomerates of glibenclamide with additives (polyethylene glycol 6000, polyvinyl pyrrolidone, β cyclodextrin, eudragit RS100, low acyl gellan gum and xanthan gum) were prepared by emulsion solvent diffusion method. Agglomerates were prepared using methanol, chloroform and water as good solvent, bridging liquid and poor solvent respectively. Particle size, flowability, compactibility and packability of plane and agglomerates with additives except with polyvinyl pyrrolidone were preferably improved for direct tabletting compared with raw crystals of glibenclamide. These improved properties of spherically agglomerated crystals were due to their large and spherical shape and enhanced fragmentation during compaction which was well supported by increased tensile strength and less elastic recovery of its compact. Also significant improvement was observed in solubility and dissolution rate of plane and agglomerates with additives except with polyvinyl pyrrolidone, over the raw crystals of glibenclamide. X-ray powder diffraction, differential scanning calorimetry and fourier transforms Infrared spectroscopy studies were indicated no any interaction of glibenclamide during agglomeration, well supported by stability studies.

(Received June 2, 2011; accepted October 3, 2011)

Keywords: Emulsion solvent diffusion, compressibility, glibenclamide, spherical crystallization

1. Introduction

Spherical crystallization is a particle design technique by which recrystallization and agglomeration can be carried out simultaneously in one step which has been successfully utilized for improvement of flowability and compactibility of crystalline drugs [1]. The use of spherical crystallization technique appears to be efficient alternative for obtaining suitable particles for direct compression [2]. In consequence of such modifications in the crystal habit, certain parameters like bulk density, flow property, compactibility, dissolution rate, stability can also be changed [3]. Spherical agglomeration (SA) can be carried out using various methods like spherical agglomeration, emulsion solvent diffusion (ESD), ammonia diffusion and neutralization [4]. Among which the SA and ESD methods are widely employed. In SA method nearly saturated solution of the drug in the good solvent is poured into the poor solvent, provided the miscibility between the poor and good solvent is stronger than the affinity between the drug and good solvent. The bridging liquid which accelerates the coalescence should be immiscible with the poor solvent and should preferentially wet the precipitated crystals [5]. In ESD method the drug is dissolved in the good solvent and bridging liquid and the resultant solution is dispersed into the poor solvent producing emulsion (quasi) droplets, even though the pure solvents are miscible. In this method

---

[*] Corresponding author: sachinpatil79@rediffmail.com

the affinity between the drug and good solvent is stronger than that of good solvent and poor solvent. The good solvent diffuses gradually out of the emulsion droplets into the surrounding poor solvent phase and the poor solvent diffuses into the droplets by which a drug crystallizes inside the droplets [6]. Glibenclamide (GLM) is oral antidiabetic used in the management of type II diabetes mellitus. It is rapidly absorbed after oral administration with plasma half life 5.05 h [7]. Aim of the present investigation was to improve micromeritic properties, flowability, compactibility, packability, solubility and drug release of GLM by ESD method with additives for direct compression.

2. Experimental

2.1. Materials

Glibenclamide (GLM) and β cyclodextrin (β-CD) were kindly provided by Alembic research Centre, Gujarat, India. Low acyl gellan gum (GG) and xanthan gum (XG) were kindly provided by C.P. Kelco Pvt. Ltd. Mumbai (India). Eudragit RS 100 (EU), polyethylene glycol 6000 (PEG), polyvinyl pyrrolidone (PVP), methanol and chloroform were purchased from Rajesh chemicals, Pune, India. All chemical used were of analytical grade.

2.2. Methods

2.2.1. Development of spherically agglomerated crystals of GLM by ESD method:

GLM (10 g) was dissolved in a mixture of 60 ml methanol (good solvent) and 40 ml chloroform (bridging liquid). The resultant solution was poured in to 500 ml of distilled water (poor solvent) containing 1 % w/v of PEG/PVP/β-CD/EU/GG/XG with stirring at 800 revolutions per minute (rpm) for 20 minutes at 25°C. One batch was prepared without additives in poor solvent (plane agglomerates). The obtained recrystallized agglomerates were collected by vacuum filtration and dried in oven at 60° C for 4 hours (hrs). The dried crystals were stored in a dessicator at room temperature before use. Above process was repeated several times to obtain enough materials for characterization and to observe repeatability. Formulation codes were given for drug, plane agglomerates, agglomerates with PEG, β-CD, EU, GG, XG and PVP as A, B, C, D, E, F, G and H respectively.

2.2.2. Determination of Yield and Drug content:

Yield of the prepared agglomerates were determined by weighing the agglomerates after drying using equation 1.

$$\text{Yield} = (\text{Practical Weight}/\text{Theoretical Weight}) \times 100 \qquad (1)$$

For determination of drug content spherical agglomerates of GLM equivalent to 100 mg of GLM were triturated and dissolved in a solvent system with methanol: water: hydrochloric acid 250:250:1 ml. Appropriately diluted samples were filtered through Whatman filter paper 41(pore size 25 µm) and drug content was determined spectrophotometrically at 300 nm using UV-Visible spectrophotometer, Jasco V530 (Jasco Japan). Percentage drug content was calculated using equation 2.

$$\text{Drug Content} = (\text{Practical Drug Concentration} / \text{Theoretical Drug Concentration}) \times 100 \qquad (2)$$

2.2.3. Micrometric properties of raw crystals and spherical agglomerates:

Mean particle size of GLM and its agglomerates was determined by randomly counting average diameter of 100 particles with optical microscope and their microphotographs were taken. Micrometric properties of raw crystals and spherical agglomerates were determined. Particle size was determined by microscopy method. Bulk density and tap density was determined by tap density tester (Dolphin^{TM}) and Carr's index, Hausners were calculated accordingly. The flow behavior of raw crystals and spherical agglomerates was determined by Angle of repose using fixed funnel method [8].

2.2.4. Compaction behavior of raw crystals and spherical agglomerates:

The Heckel equation is widely used to evaluate the volume reduction of the materials when pressure is applied during compression and is as given in equation 3 [9].

$$ln\ (1/1\text{-}D) = KP + A \tag{3}$$

Where D is the relative density of powder for applied pressure P. The slope of the straight-line portion K is the reciprocal of the mean yield pressure (MYP) of the material. From the value of the intercept A, the relative density D_a, D_o and D_b can be calculated using equation 4, 5 and 6 respectively.

$$D_a = 1\text{- } e^{-A} \tag{4}$$

$$D_o = 1\text{- } e^{-Ao} \tag{5}$$

$$D_b = D_a - D_o \tag{6}$$

Where A_o represents the intercept of the line when P = 0. The Heckel study was performed by compressing 500 mg of raw crystals and spherical agglomerates on hydraulic press (Samrudhi Enterprises, Mumbai, India.) using 13 mm flat faced punch and die set, at pressure 20, 30, 40, 60, 80, 100 and 120 kN and thickness, weight and diameter of compacts were determined. For determination of ER thickness of the compact of agglomerates and raw crystal of GLM was determined at compression pressure 60 kN and at 24 hrs after releasing the tablet. ER was calculated in equation 7 [10].

$$ER = [(t_2 - t_1)\ /t_1] \tag{7}$$

Where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness of the recorded tablet. Crushing strength was measured immediately after compression with a tablet strength tester (Erweka, type TBH 30, Germany). Tensile strength Q was calculated in equation 8 [11].

$$Q = 2H\ /\ (\ \pi\ d\ t\ ) \tag{8}$$

Where H is the tablet crushing strength, d is the diameter and t is the thickness of the tablet.

2.2.5. Packability determination:

In packability determination 25 g of sample was poured slowly and gently into a 25 ml measuring cylinder and tapped for 100, 200, 300, 400, 500, 600, 700, 800, 1100 and 1200 times. The Stampfvolumeter measurements allow calculations of the compactibility and cohesiveness values via modified Kawakita’s equation (equation 9) [12] and Kuno’s equation (equation 10) [13].

$$(\mathrm{n}/C) = (1/ab) + (n/a) \tag{9}$$

Where, $C = (V_o - V_n)/V_o$, $a = (V_o - V_\infty)/V_o$, n = number of tapping, C = difference in volume (degree of volume reduction), a and b = constant for packability and flowability, V_o = initial volume, V_n = final volume after nth tapping, and V_∞ = powder bed volume at equilibrium. The slope $1/a$ and intercept $1/ab$ of plot n/C verses n gives the compactibility constant a, flowability constant b and cohesiveness $1/b$. The value of k in Kunos equation was determined directly putting the values of the densities in the equation 10.

$$\rho_f - \rho_n = (\rho_f - \rho_o)\ e^{-kn} \tag{10}$$

Where, ρ_f, ρ_o, ρ_n are apparent densities at equilibrium, initial state and n^{th} tapped, respectively.

2.2.6. Solubility study:

Solubility of raw crystals and spherical agglomerates of GLM were determined in distilled water and in pH 8 phosphate buffer. Excess amount of sample were added in 20 ml of distilled water / pH 8 phosphate buffer and were continuously shaken (300 rpm) at 25 ± 0.5°C for 48 h and sonicated using sonicator (Dolphin^{TM}) for 2 h. Samples were filtered through 0.45 µm filters and assayed spectrophotometrically for drug content at 300 nm.

2.2.7. X-ray powder diffraction (XRPD):

X-ray powder diffraction of raw crystals and spherical agglomerates were analyzed by Philips PW 1729 x-ray diffractometer. Samples were irradiated with monochromatized Cu K_α – radiations (1.542 A°) and analyzed between 2-60° (2θ). The voltage and current used were 30kV and 30 mA respectively. The range was 5 x 10^3 cycles/s and the chart speed was kept at 100 mm/2θ.

2.2.8. Differential Scanning calorimetry (DSC):

Thermal properties of raw crystals and spherical agglomerates of GLM were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). Indium standard was used to calibrate the DSC temperature and enthalpy scale. Nitrogen was used as the purge gas through DSC cell at flow rate of 50 ml per min and 100 ml per min through the cooling unit. The sample (5-10mg) was heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 0 to 300°C at a heating rate of 10°C/ min.

2.2.9. Fourier transforms Infrared spectroscopy (FT-IR):

FTIR of raw crystals and spherical agglomerates of GLM was recorded using Jasco V5300 (Jasco, Japan) FT-IR system using potassium bromide (KBr) pellet method. Each spectrum was derived from single average scans collected in the region 4000 to 500 cm^{-1}.

2.2.10. In-Vitro dissolution studies:

The dissolution studies raw crystals and spherical agglomerates of GLM were performed by using USP 26 type II dissolution test apparatus (Dolphin^{TM}, Mumbai, India) in 900 ml of pH 8 phosphate buffer. Temperature was maintained at 37 ± 2°C and 100 rpm stirring was provided for each dissolution study. GLM and its spherical agglomerates equivalent to 100 mg of GLM were used for each dissolution study. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41(pore size 25 µm), concentration of GLM was determined spectrophotometrically at 300 nm on UV-Visible spectrophotometer Jasco V530 (Jasco, Japan).

2.2.11. Stability studies

All spherical agglomerates of GLM were charged for the accelerated stability studies as per ICH guidelines (40 ± 2 °C C and75 ± 5% RH) for a period of 6 months in a stability chamber (Thermolab, Mumbai, India). The samples were placed in vials with bromobutyl rubber plugs and sealed with aluminum caps. The samples were withdrawn at 30, 60, 90 and 180 days and evaluated for the drug content and *in vitro* drug release for 30 min.

2.2.12. Statistical analysis:

Results are expressed as mean ± S.D for triplicate samples. The results were statistically analyzed and significant differences among formulation parameters were determined by one-way analysis of variance using ‘Graph Pad Instate$^{®}$’Version 3.05 (USA), statistical analysis program. Statistical significant was considered at $p < 0.05$.

3. Results and discussion

3.1. Development of spherically agglomerated crystals of GLM by ESD method:

Selection of good solvent, poor solvent and bridging liquid was done on the basis of the miscibility of the solvents and the solubility drug in individual solvents. Since, GLM is soluble in methanol, slightly soluble in chloroform but insoluble in water [14], methanol, chloroform and water were used as good solvent, bridging liquid and poor solvent respectively. Preliminary experiments were performed to optimize the concentration of solvents. In absence of bridging liquid the system produced agglomerates rich of needle shaped crystals. At optimized concentration of good solvent and bridging liquid (3:2) different stirring rates were tested and an optimum was found to be 800 rpm. Formation of lumps, agglomerates of un-uniform size and shape was observed at lower stirring rates, while high stirring rate destroyed the agglomerates. When solution of drug in good solvent and bridging liquid was poured into poor solvent the quasi-emulsion droplets of drug solution were produced initially. Successively the crystallization of a drug occurred at the outer surface of the droplet. The spherically agglomerated crystals were produced simultaneously after complete crystallization and the whole process is called as emulsion solvent diffusion. Under stirring the agglomerates were spheronized and compacted. Yield and drug content of the GLM agglomerates was found satisfactory as given in table 1.

3.2. Micrometric properties of raw crystals and spherical agglomerates:

Agglomerates formed were spherical having micrometric properties given in table 1. It was found that particle size of plane agglomerates and agglomerates with additives except PVP was increased more than 10 times than original crystals may be due to particle agglomeration. Microphotographs of drug, plane agglomerates and agglomerates with additives shown in figure 1 revealed that the agglomerates were spherical with smooth surface. The bulk density of plane agglomerates and agglomerates with additives except PVP was lower than raw crystals of GLM. Reduction in bulk densities of spherical agglomerates indicates the greater porosity within the agglomerates [15]. Angle of repose, Carr’s index and Hausners ratio values of the plane agglomerates and agglomerates with additives except PVP was lower than raw crystals of GLM, indicates its better flowability, might be due to large and spherical shape of agglomerates clearly indicated in SEM microphotographs of the agglomerates.

Table 1: Micrometric properties of raw crystals and spherical agglomerates of GLM.

Formulation Codes	**Yield (%) (n=3)**	**Drug content (%) (n=3)**	**Average diameter (µm) n=100**	**Angle of repose (°) (n=3)**	**Bulk density (g/cc) (n=3)**	**Tap density (g/cc) (n=3)**	**Carr’s Index (%) (n=3)**	**Hausners ratio (n=3)**
A	-	-	14.7 ± 1.1	52.23 ± 0.87	0.322 ± 0.02	0.476 ± 0.03	32.35 ± 1.3	1.42 ± 0.06
B	97 ± 2	93 ± 2	159.3 ± 1.1	23.14 ± 0.79	0.281 ± 0.01	0.331 ± 0.04	15.01 ± 1.1	1.18 ± 0.03
C	96 ± 1	94 ± 1	148.5 ± 1.0	22.23 ± 0.88	0.279 ± 0.04	0.325 ± 0.06	14.15 ± 1.0	1.16 ± 0.05
D	96 ± 1	92 ± 3	153.7 ± 1.2	23.23 ± 0.44	0.275 ± 0.03	0.320 ± 0.08	14.06 ± 1.3	1.16 ± 0.07
E	95 ± 2	93 ± 2	141.5 ± 1.3	24.13 ± 0.39	0.271 ± 0.06	0.319 ± 0.03	15.04 ± 0.9	1.17 ± 0.02
F	97 ± 2	94 ± 1	143.5 ± 1.2	26.12 ± 0.98	0.276 ± 0.05	0.322 ± 0.07	14.28 ± 1.3	1.16 ± 0.07
G	95 ± 1	90 ± 2	147.5 ± 1.0	21.21 ± 0.67	0.269 ± 0.04	0.331 ± 0.09	18.73 ± 1.1	1.23 ± 0.08
H	91 ± 3	87 ± 2	16.4 ± 1.1	39.23 ± 0.35	0.332 ± 0.07	0.483 ± 0.02	31.26 ± 1.4	1.45 ± 0.04

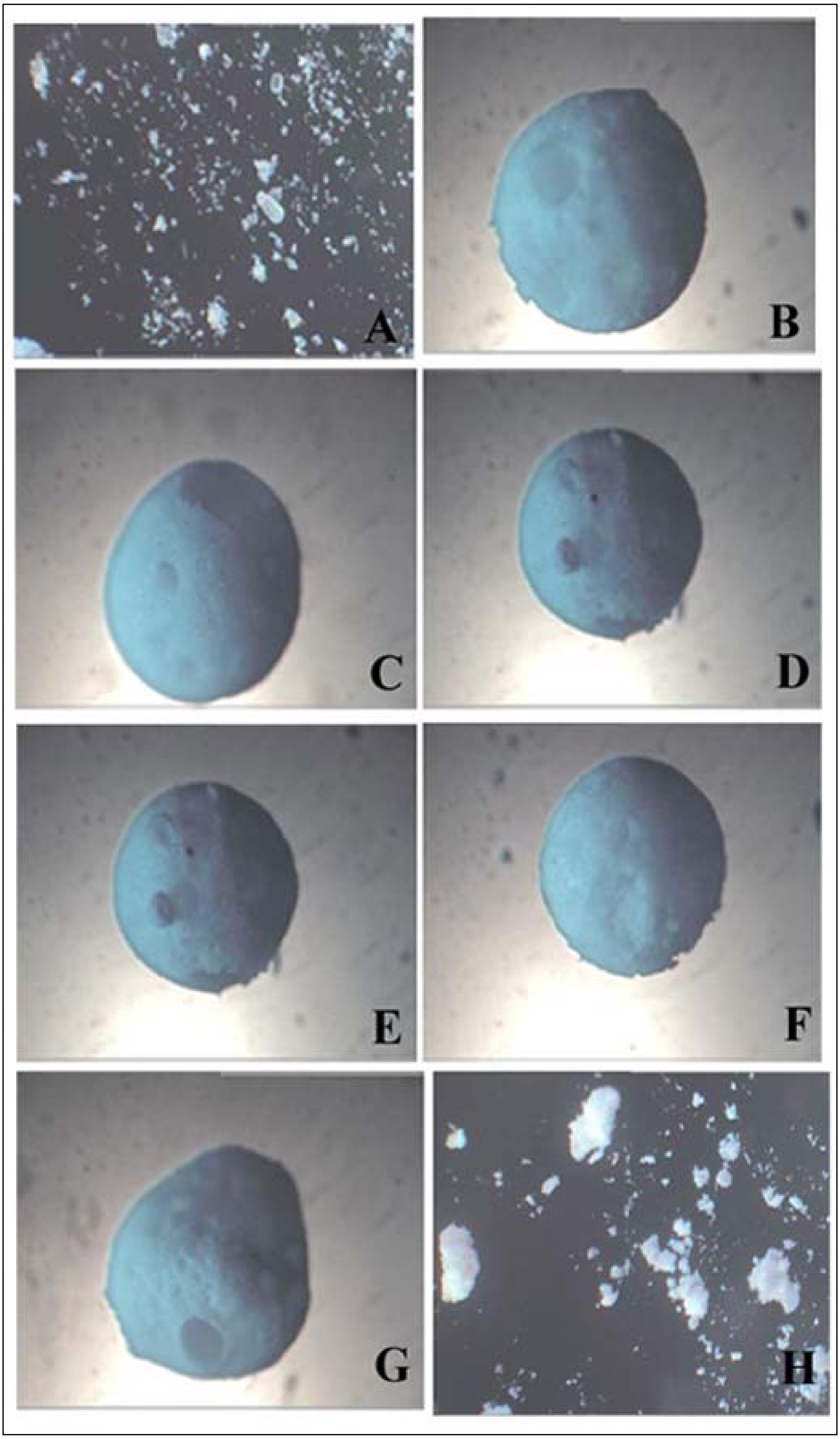

Fig. 1. Microphotographs of Glibenclamide and its Spherical agglomerates.

PVP has most effectively decreased the average diameter in the resultant agglomerates might be due to adsorption on the surface of crystals and preventing their growth resulting in fine crystals [15]. Angle of repose, Carr's index and Hausners ratio values of agglomerates with PVP has shown its poor flowability. In case of agglomerates with PEG, β-CD, EU, GG and XG average diameter was increased than raw crystals but decreased than plane agglomerates of GLM. These findings suggests that these additives were poorly adsorbed at the surface which reduces the interfacial tension between bridging liquid and crystals and decreases the adhesive force acting to agglomerate the crystals [16].

3.3. Compaction behavior of raw crystals and spherical agglomerates:

The compressibility of a material is its ability to reduce in volume as a result of an applied pressure. Heckle parameters D_a, D_o, D_b, *MYP* and *ER* of raw crystals and spherical agglomerates of GLM were given in table 2. D_b value represents the particle rearrangement phase in early compression stage and tends to indicate extent of particle fragmentation. The D_b values for plane agglomerates and agglomerates with PEG, β-CD, EU, GG and XG were higher than the raw crystals of GLM indicated that the agglomerates were highly fractured during early stage of compression although fragmentation is followed by plastic deformation. The results were well supported by higher *MYP* values. The elastic recoveries of the compacts of plane agglomerates and agglomerates with PEG, β-CD, EU, GG and XG were smaller than that of original drug crystals. These findings suggested that the agglomerated crystals were easily fractured, and the new surface of crystals produced might contribute to promote plastic deformation under compression. Lower D_b value of agglomerates with PVP than other agglomerates might be attributed to its small particle size. Compactibility of samples was evaluated based on the tensile strengths of the compacts compressed at different compaction pressures. The tensile strength of tablets prepared with agglomerated crystals and raw crystals of GLM were plotted as a function of compression pressure shown in figure 2. It was found that the tensile strength of tablets with plane agglomerates and agglomerates with PEG, β-CD, EU, GG and XG were dramatically increased indicating enhanced fragmentation during compression resulting in increased D_b. Tablet with raw crystals of GLM and agglomerates with PVP showed lower tensile strength may be due to presence of capping. The high tensile strengths of the tablets are indicative of stronger interparticulate bonding between the agglomerates. The improved compactibility of agglomerates might be attributed to characteristic structure responsible for the large relative volume changes during the early stage of the compression process due to their fragmentation. It has been shown that a reduction in bulk density of agglomerates results in an increase in the tensile strength of tablets, similar results were obtained in study by Ali N et.al [15].

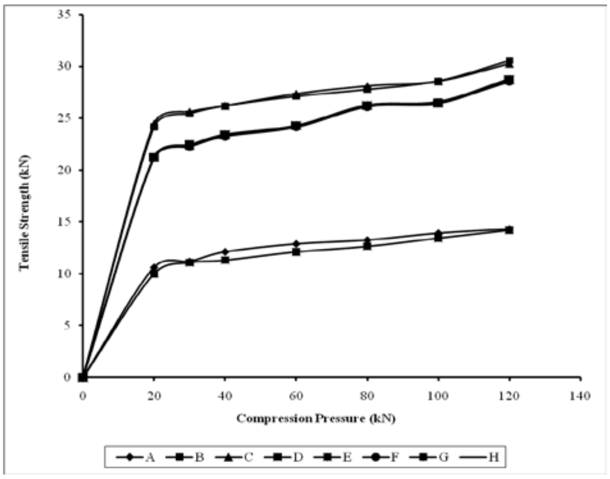

Fig. 2. Plot of tablet tensile strength as a function of compression pressure for glibenclamide and its Spherical agglomerates.

Table 2. Heckel parameters D_a, D_o, D_b, MYP (mean yield pressure) and ER (elastic recovery) of raw crystals and spherical agglomerates of GLM. (n=3) (FC: Formulation Codes).

FC	D_a	D_o	D_b	*MYP*	*% ER*
A	0.537 ± 0.003	0.378 ± 0.011	0.159 ± 0.007	21.54± 2.4	7.8 ± 1.2
B	0.421 ± 0.002 ***	0.185± 0.003 ***	0.236 ± 0.005 **	25.41± 1.8 **	4.8 ± 0.4 ***
C	0.578 ± 0.003 ***	0.192± 0.004 ***	0.386 ± 0.003***	26.31± 1.6 **	4.3 ± 0.6 ***
D	0.489 ± 0.005 ***	0.171± 0.008 ***	0.318 ± 0.003***	27.31± 2.3 **	4.9 ± 0.5 ***
E	0.582 ± 0.002 ***	0.185± 0.003 ***	0.397 ± 0.004***	29.31± 1.5 **	5.4 ± 0.7 ***
F	0.578 ± 0.004 ***	0.186± 0.007 ***	0.392 ± 0.005***	32.31± 1.2 **	5.1 ± 0.8 ***
G	0.569 ± 0.005 ***	0.188± 0.006 ***	0.381 ± 0.003***	31.31± 1.7 **	4.5 ± 0.4 ***
H	0.612 ± 0.010 *	0.396± 0.006*	0.216 ± 0.006 **	20.31± 2.9 *	7.3 ± 0.8*

Significantly different from the value for raw crystals of GLM at $p < 0.001$ (***), $p < 0.01$ (**) and $p < 0.05$ (*).

3.4. Packability determination:

The packability parameters *a*, *b* and *k* obtained from Kawakita's and Kuno's equation respectively were given in table 3. It was found that for plane agglomerates and agglomerates with PEG, β-CD, EU, GG and XH, value of parameter *a* in Kawakita's equation reduced and respective parameters *b* and *k* in Kawakita's and Kuno's equation increased compared with those of raw crystals of GLM and its agglomerates with PVP. These findings proved that packability of plane agglomerates and agglomerates with PEG and β-CD were preferably improved for direct tabletting than those of raw crystals and its agglomerates with PVP. It suggests that during tabletting these agglomerates were flow smoothly from the hopper into die cavity to attain uniformity in weight and is necessary in direct tabletting. This improvement in packability and flowability is attributed to size enlargement and spherical shape of these agglomerates.

3.5. Solubility study:

Solubility of raw crystals and spherical agglomerates of GLM were given in table 3. It was observed that solubility of spherical agglomerates was increased than raw crystals of GLM. It was higher for β-CD agglomerates and lower for PVP agglomerates might be due the reason that hardly any agglomeration had occurred with PVP.

Table 3. Kawakita constants a, b, Kuno's constant k and solubility for raw crystals and spherical agglomerates of GLM. (n=3) (FC: Formulation Codes, PB: Phosphate Buffer).

FC	*a*	*b*	*k*	Solubility (μg/ml)	
				Water	**P. B. pH 8**
A	0.454 ± 0.06	0.00404 ± 0.0005	0.00304 ± 0.001	22.76 ± 1.2	98.34 ± 2.3
B	0.278 ± 0.05	0.03546 ± 0.003	0.01786 ± 0.006	74.56 ± 1.6 ***	212.32 ± 3.1 ***
C	0.295 ± 0.06	0.01285 ± 0.004	0.01432 ± 0.004	84.12 ± 2.1 ***	243.61 ± 2.1 ***
D	0.279 ± 0.03	0.01124 ± 0.006	0.01346 ± 0.006	93.24 ± 1.8 ***	398.76 ± 4.3 ***
E	0.285 ± 0.02	0.02635 ± 0.003	0.01176 ± 0.003	84.76 ± 1.1 ***	248.135 ± 3.2 ***
F	0.298 ± 0.04	0.02147 ± 0.006	0.01158 ± 0.007	63.54 ± 2.2 ***	222.32 ± 2.6 ***
G	0.304 ± 0.03	0.02964 ± 0.009	0.010938 ± 0.008	69.32 ± 1.9 ***	237.48 ± 2.9 ***
H	0.443 ± 0.07	0.00374 ± 0.0006	0.002952 ± 0.003	47.44 ± 1.4 **	141.27 ± 1.6 **

Significantly different from the value for raw crystals of GLM at $p < 0.001$ (**), $p < 0.01$ (**) and $p < 0.05$ (*)

3.6. X-ray powder diffraction (XRPD):

XRPD of raw crystals and spherical agglomerates of GLM were shown in figure 3. It has been observed that the XRPD of raw crystals and all spherical agglomerates were same which has indicated that no any polymorphic has occurred during recrystallization of GLM.

3.7. Differential Scanning Calorimetry (DSC):

DSC thermogram of raw crystals and spherical agglomerates of GLM was shown in figure 4. Crystals of GLM showed melting endotherm at 185.88 °C with heat of fusion -120 J/g and all spherical agglomerates of GLM has shown same melting endotherm and heat of fusion. These findings indicated that no any polymorphic has occurred during recrystallization of GLM.

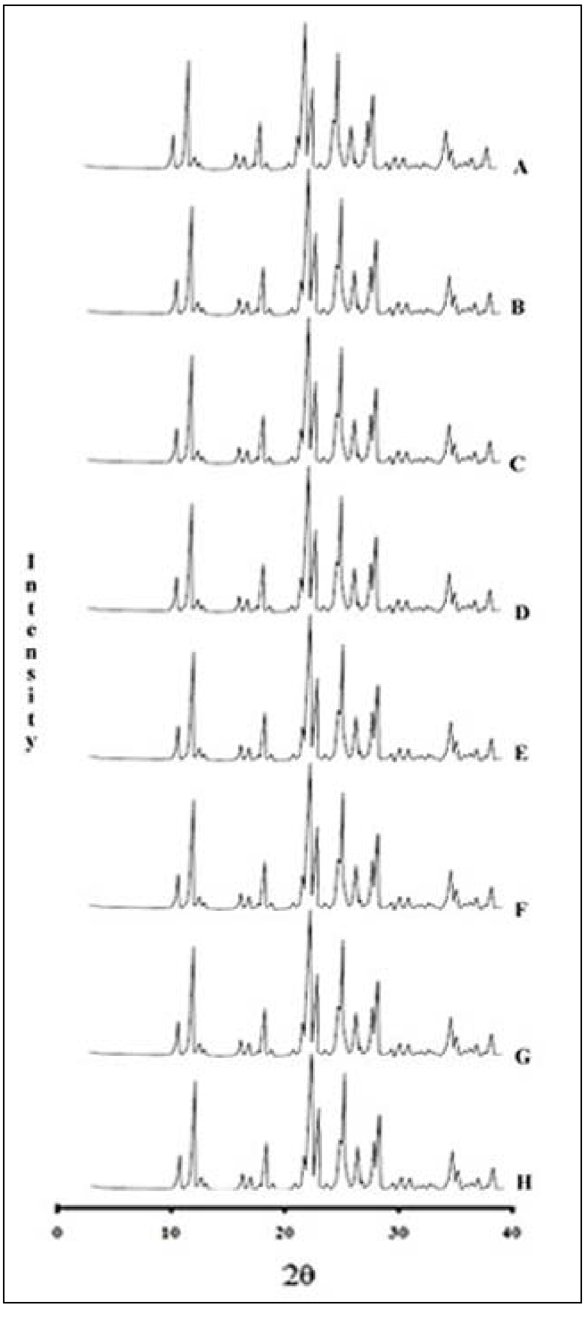

Fig. 3: XRPD spectra of Glibenclamide and its Spherical agglomerates.

3.8. Fourier transforms Infrared spectroscopy (FT-IR):

Raw crystals of GLM and spherical agglomerates of GLM exhibited identical IR spectra as shown in figure 5. It revealed that no any chemical transition has occurred during recrystallization of GLM.

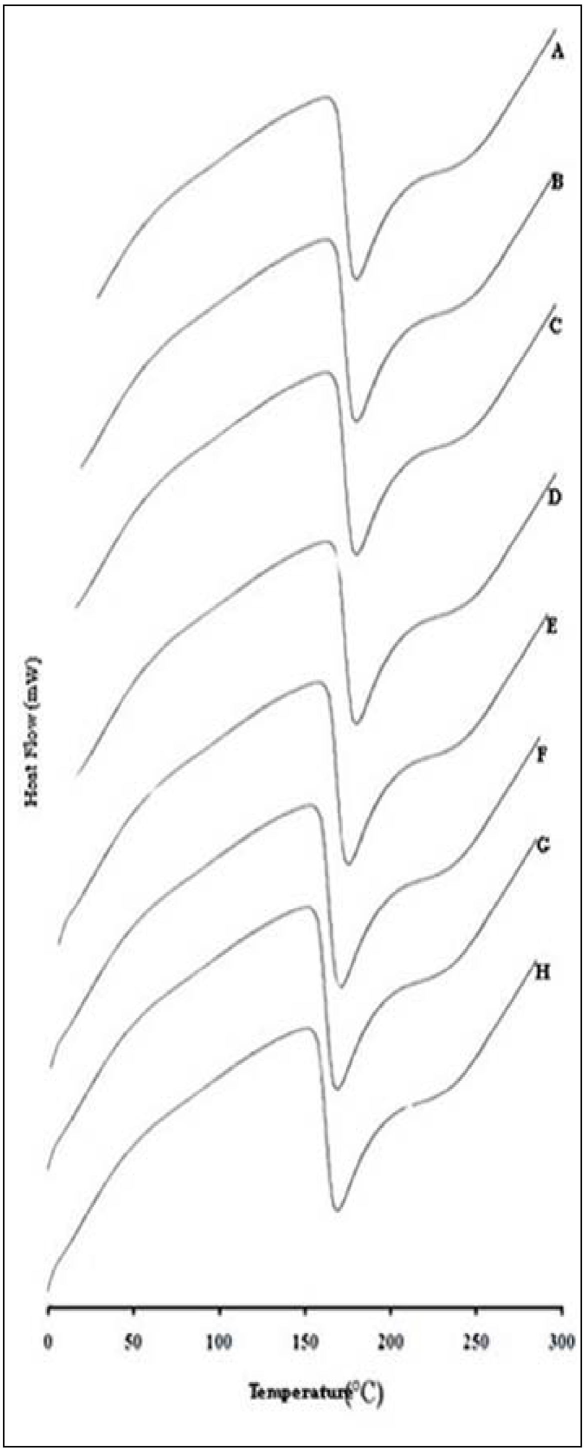

Fig. 4: DSC thermograms of Glibenclamide and its Spherical agglomerates.

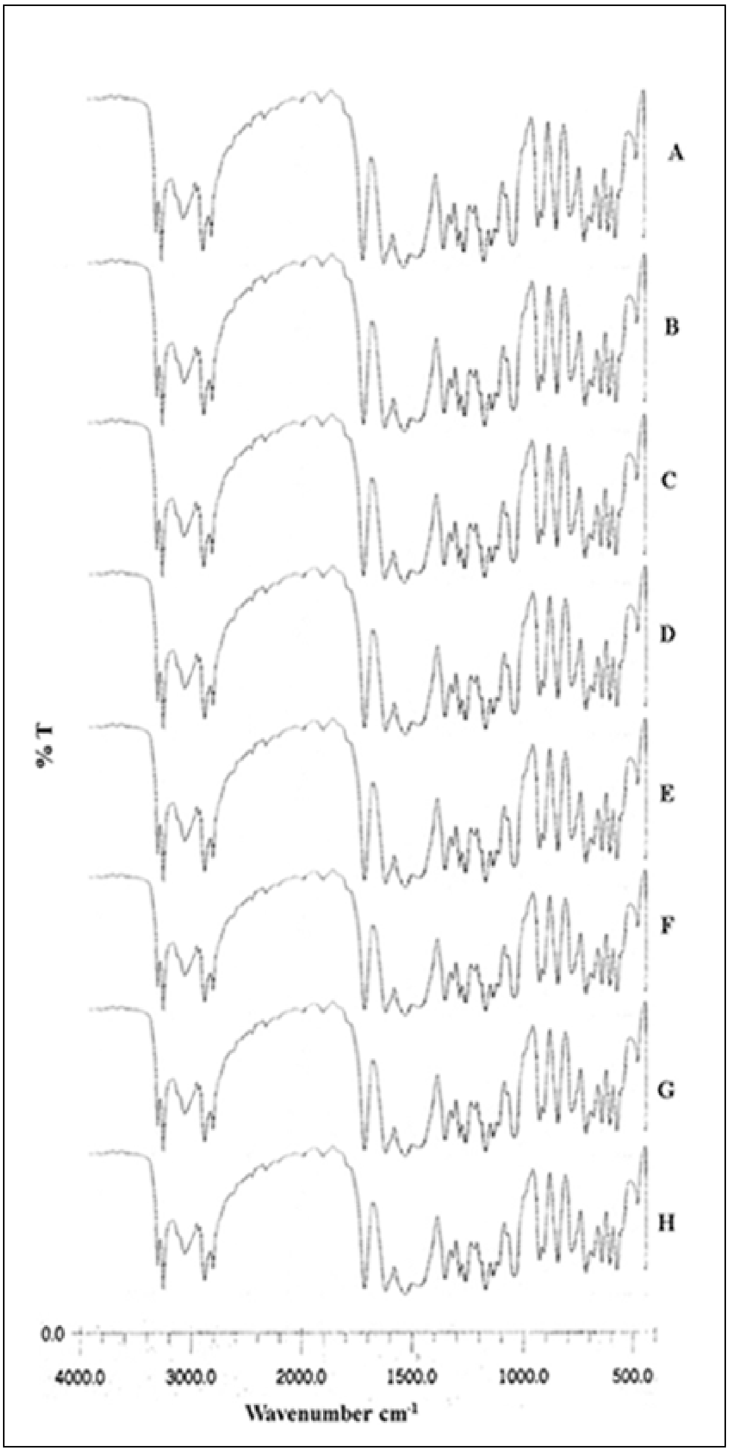

Fig. 5: IR Spectra of Glibenclamide and its Spherical agglomerates.

3.9. In-Vitro dissolution studies:

Rate of dissolution of raw crystals and spherical agglomerates of GLM were shown in figure 6. It was observed that for raw crystals of GLM up to 67 % drug was released in 30 min while for agglomerates of GLM drug release was increased with the order β-CD > PEG > EU > XG > GG > plane > PVP > raw crystals may be due to increased wettability and porosity.

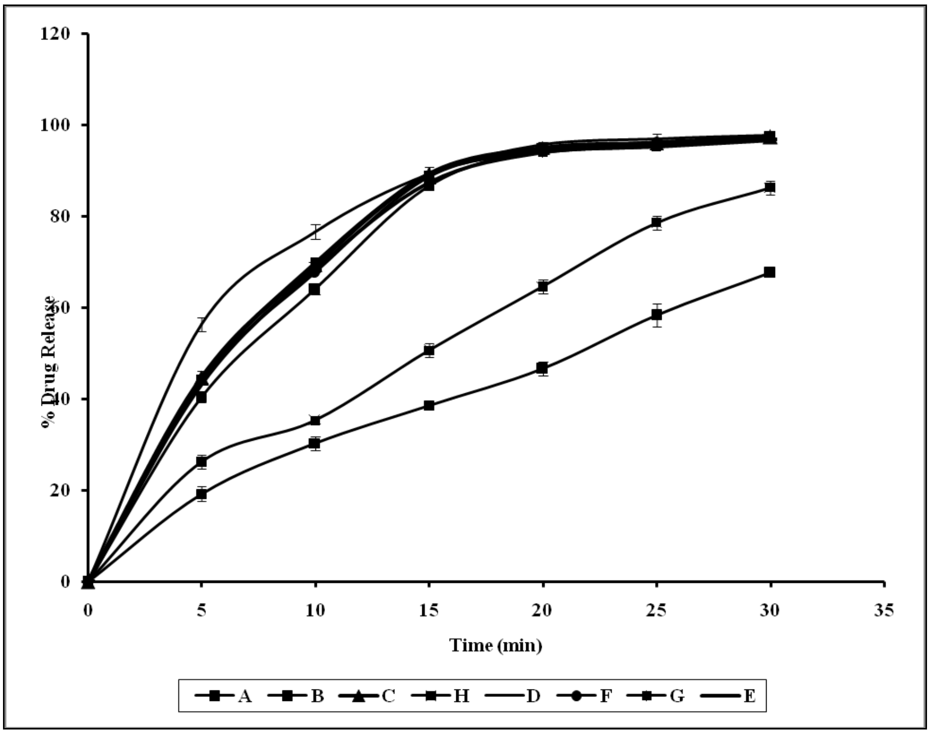

Fig. 6: Dissolution study of A: glibenclamide and Spherical agglomerates of GLM: B: Plane, C: with PEG, D: with β-CD, E: with EU, F: with GG, G: with XG, H: with PVP.

3.10. Stability studies:

The agglomerates did not show any significant change in drug content and *in vitro* drug release during stability study as given in table 5. It has indicated that the prepared agglomerates were adequately stable as per regulatory requirements.

Table 4: Stability study data of spherical agglomerates of GLM. (n=3).

Formulation Codes	**0 Days**		**30 Days**		**60 Days**		**90 Days**		**180 Days**	
	Drug Content (%)	**Drug Release (%)**	**Drug Content (%)**	**Drug Release (%)**	**Drug Content (%)**	**Drug Release (%)**	**Drug Content (%)**	**Drug Release (%)**	**Drug Content (%)**	**Drug Release (%)**
B	93 ± 2	88.3 ± 1	92 ± 2	86.7 ± 1	90 ± 2	86.8 ± 1	91 ± 1	85.1 ± 2	90 ± 1	84.9 ± 3
C	94 ± 1	93.3 ± 1	92 ± 1	93.8 ± 1	92 ± 2	93.1 ± 1	92 ± 1	92.1 ± 1	91 ± 2	91.9 ± 2
D	92 ± 3	95.6 ± 1	91 ± 2	94.4 ± 1	89 ± 3	92.6 ± 1	92 ± 1	92.1 ± 1	91 ± 1	91.8 ± 2
E	93 ± 2	92.3 ± 1	92 ± 2	91.3 ± 1	92 ± 2	91.1 ± 1	92 ± 1	88.3 ± 2	90 ± 2	89.1 ± 1
F	94 ± 1	91.6 ± 1	93 ± 1	91.8 ± 1	91 ± 2	90.9 ± 1	91 ± 1	90.1 ± 1	90 ± 1	89.3 ± 1
G	90 ± 2	89.6 ± 2	89 ± 2	88.1 ± 2	89 ± 1	87.8 ± 3	89 ± 2	88.8 ± 1	88 ± 2	87.0 ± 1
H	87 ± 2	83.3 ± 3	86 ± 3	82.3 ± 2	85 ± 1	81.5 ± 2	82 ± 2	81.7 ± 1	80 ± 1	78.1 ± 2

No significant different from the values of 0 days as $p > 0.1$ for all agglomerates.

4. Conclusion

Stable spherical crystals of GLM were successfully prepared by emulsion solvent diffusion method. Flowability, compactibility and packability were dramatically improved for plane agglomerates and agglomerates with PEG and β-CD compared with raw crystals of GLM resulting in successful direct tabletting without capping. Whereas, agglomerates of GLM with PVP has shown poor flowability, compactibility and packability. Also remarkable fragmentation, increased tensile strength of plane agglomerates and agglomerates with additives except with PVP indicates improved compactibility. Improved solubility and dissolution of plane agglomerates and agglomerates with PEG, β-CD, EU, GG, XG than raw crystal and PVP agglomerates of GLM has shown their improved wettability. During agglomeration no any polymeric and chemical transition has. It concludes that spherical crystallization of GLM with selective additives is a satisfactory method to improve flowability, compactibility and packability for direct tabletting along with solubility and dissolution.

Acknowledgments

The authors are thankful to Alembic research Centre, Gujarat, India, for providing free gift sample of glibenclamide and β cyclodextrin. The authors are also thankful to Head of the Department, University Department of Pharmaceutical Sciences, Utkal University, Bhubaneswar, Orissa, India and the Principal, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Dist. Satara, Maharashtra, India for providing research facility.

References

[1] S. V. Patil, S. K. Sahoo. Research J. Pharm. and Tech., **2**, 234 (2009).
[2] A. R. Paradkar, A. P. Pawar, K. R. Mahadik K, S. S. Kadam. Indian Drugs, **31**, 229 (1994).
[3] D. Tanguy, P. Marchal. 13th Symposium on Ind. Cryst., Toulouse, September **16–19**, 715 (1996).
[4] A. R. Paradkar, A. P. Pawar, J. K. Chordiya, V.B. Patil, A. R. Ketkar. Drug. Dev. Ind. Pharm., **28**, 1213 (2002).
[5] Y. Kawashima, M.Okumura, H. Takenaka. Science, **216**, 1127 (1982).
[6] F. Espitalier, B. Biscans, J. R. Authelin.C. Laguerie. (1997). Chemical Engineering Research and Design. **75**(2): 257 (1997).
[7] S. Sweetman, Martindale: The extra pharmacopoeia, 17th ed., London, 333 (2003).
[8] L. Lachman, H. A. Liberman, J. L. Konig. Theory and Practice of Industrial Pharmacy, 3rd ed., Philadelphia, 317 (1986)
[9] R. W. Heckel. Trans. Metal Sci. AIME, **221**, 671 (1961)
[10] N. A. Armstrong, R. F. Hainess-Nutt. Powder Technol., **9**, 287 (1974).
[11] J. T. Fell, J. M. Newton. J. Pharm. Sci. **5**, 688 (1970).
[12] K. Kawakita, K. H. Ludde. Powder Technol., **4**, 61 (1970).
[13] T. Kuno, G. Jimbo, E. Saito, H. Takahashi, S. Hayakawa. Powder Theory and Application, Tokyo, 341–346 (1979).
[14] J. Maryadele. The Merck Index, 13th ed., New York, 1335 (2001).
[15] N. Ali, M. Maryam, H. Z. Davood, B. J. Mohammad. Powder Technol., **175**, 73 (2007).
[16] Y. Kawashima, T. Handa, H. Takeuchi, M. Okumura, H. Katou, O. Nagata. Chem. Pharm. Bull., **34**, 3376 (1986).