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Research Article

Directly Compressible Glibenclamide Tablet Prepared from Spherical Agglomerates: A Comparative Evaluation with Marketed Tablet

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Abstract

Agglomerates were prepared using methanol, chloroform and water as good solvent, bridging liquid and poor solvent, respectively. Direct compressible tablets of the agglomerates showed appropriate hardness, friability, weight variation and disintegration time with improved drug release than conventional marketed tablets. Tablets were adequately stable as per regulatory guidelines. Pharmacokinetic study indicated rapid absorption with higher bioavailability of the drug from the prepared tablets of agglomerates than marketed tablet (Glyburide; Sandoz).
Hence, the tablets prepared with the agglomerates of glibenclamide may reduce the total dose of drug and could improve the patient compliance by reducing the dose-related side effects.

Keywords: Directly compressible tablet, glibenclamide, spherical crystallization, bioavailability, stability

Introduction

In recent time pharmaceutical industry needs efficient, time and cost saving method in manufacturing. Specifically for tablet direct tableting is such method as it involves simply mixing and compression of powder.[1] But it strongly depends on the compressibility of the drug crystals used otherwise lot of excipients are necessary resulting in bigger sized tablets. Usually fine crystals are preferred over large crystals of poorly soluble pharmaceuticals as they offer better bioavailability. However, micronizations of crystals often avert efficient powder processing due to poor flowability, compactibility and packability. Spherical crystallization technique comes out to be competent option for obtaining appropriate particles for direct compression. The spherical crystallization technique has already been successfully used to improve the tabletbility of several drugs.[2] Different methods are reported in the literature to produce spherical agglomerates such as spherical agglomeration (SA), emulsion solvent diffusion (ESD), ammonia diffusion and neutralization. Among which the SA and ESD methods are widely employed.[3-5]

In previous study we had prepared the spherical agglomerates of Glibenclamide (GLM) using different additives: polyethylene glycol 6000, polyvinyl pyrrolidone, β-cyclodextrin, Eudragit RS100, low acyl gellan gum and xanthan gum.[6] The objective of this study was to prepare tablets from the spherical agglomerates of GLM by direct compression with comparatively improved drug release than marketed tablet.

Materials and Methods

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 CP Kelco, Division of JM Huber, India. Eudragit RS 100 (EU), polyethylene glycol 6000 (PEG), polyvinyl pyrrolidone (PVP), methanol and chloroform were purchased from Rajesh chemicals, Pune, India. All chemicals used were of analytical grade.

Preparation of spherical agglomerates of GLM by ESD method

GLM (10g) 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/β-CD/EU/GG/XG/ PVP with stirring at 800 rpm for 20 min 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 4h. The dried crystals were stored in desiccators 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, agglomerates without additives, agglomerates with PEG, β-CD, EU, GG, XG and PVP as A, B, C, D, E, F, G and H, respectively.

Yield, drug content and micrometric properties

Yield of the prepared agglomerates were determined by weighing the agglomerates after drying. For determination of drug content spherical agglomerates of GLM equivalent to 100 mg of GLM were triturated and dissolved in a solvent system containing methanol: water: hydrochloric acid (250:250:1, v/v). 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). 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. Bulk density and tap density were determined by tap density tester (DolphinTM) and Carr's index and Hausner's ratio were determined. The flow behavior of raw crystals and spherical agglomerates was determined by angle of repose using fixed funnel method.[7]

Preparation of GLM tablets

GLM agglomerates equivalent to 5 mg of GLM were manually mixed with directly compressible lactose (86 mg per tablet) and carmellose calcium (8 mg per tablet). The obtained blend was finally mixed with magnesium stearate (1 mg per tablet) for 1 min. Final blend (100 mg per tablet) was compressed using Rotary tablet machine with 6 mm standard concave punch. The weight variation of the tablets was determined taking weight of 20 tablets using electronic balance. Hardness, thickness, friability and disintegration time (in water) of tablets were studied by Monsanto hardness tester, vernier caliper, Roche friabilator and disintegration test apparatus, respectively.[7]

Evaluation of GLM tablets

In vitro dissolution study

The dissolution studies of raw crystals and spherical agglomerates of GLM were performed by using USP 26 type II dissolution test apparatus (DolphinTM, Mumbai, India) in 900 ml of pH 8.0 phosphate buffer.[6] Temperature was maintained at 37±2°C and 75 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[6] (UV-Visible spectrophotometer, Jasco V530, Japan).

Stability study

Accelerated stability study of tablets of GLM prepared from spherical agglomerates were carried out at 40±2°C and 75±5% RH[8] 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.

Pharmacokinetic study

The pharmacokinetic studies were carried in male Wistar rats (weighing 200-250 g) and the protocol was approved by the Institutional Animal Ethical Committee of Shree Santkrupa College of Pharmacy, Ghogaon, Maharashtra, India. (Approval No.: 1110/ac/07/CPCSEA, 24/09/2007). The overnight fasted rats were divided into 8 groups ($n = 6$) and treated as group 1: Marketed tablet of GLM and group 2 to 8: tablets of GLM agglomerates (prepared from agglomerates of batch B to H, respectively). Each rat was given a dose of 5 mg/kg orally as a solution in 0.1M citric acid with dose volume of 10 ml/kg. Subsequently blood sample (0.3 ml) was withdrawn through tail vein and collected at predetermined intervals of 0.5, 1, 1.5, 2, 4, 6 and 8 h of post-dose into heparinized tubes. The supernatant (plasma) was separated immediately using centrifugation at 3000 rpm for 15min into clean and dry test tubes and were immediately frozen (-20°C) until further study . The samples were analyzed by HPLC consisted of a dual plunger pump (LC- 10ATVP, Shimadzu, Kyoto, Japan), a UV-vis detector (SPD-10AVP, Shimadzu, Japan) with a system controller (SCL-10AVP, Shimadzu, Japan) and a RP C-18 column (Hypersil BDS C18 250 cm × 4.6 mm; 5 μm) as per the method described by Mutalik and Udupa.[9] The mobile phase was monobasic phosphate buffer (pH 3.5; 20 mM) and acetonitrile in a proportion of 60:40 (v/v). All separations were performed isocratically at a flow-rate of 1 ml/min. Column temperature was maintained at room temperature (25±2°C). The peaks were determined using a UV detector set at a wavelength of 225nm. Maximum plasma concentration (C_{max}), time needed to reach the maximum plasma concentration (T_{max}), area under the concentration– time curve (AUC), mean residence time (MRT), elimination half life ($t_{1/2}$) and elimination rate constant Ke was calculated by 'PK Solutions®', Pharmacokinetic Software for Research and Education.

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 software. Statistical significant was considered at $p < 0.05$.

Results and Discussion

Development of spherical agglomerates 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 of drug in individual solvents. Since, GLM is soluble in methanol, slightly soluble in chloroform but insoluble in water[10]; methanol, chloroform and water were used as good solvent, bridging liquid and poor solvent, respectively. 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, drug content and micrometric properties

Yield, drug content and micrometric properties of agglomerate are given in Table 1. Yield and drug content of the GLM agglomerates were found satisfactory. 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. All agglomerates (except with PVP) were spherical with smooth surface (Fig. 1). Reduction in bulk densities of spherical agglomerates indicates the greater porosity within the agglomerates.[11] Angle of repose, Carr's index and Hausner's ratio values of agglomerates indicated its better flowability which might be due to large and spherical shape of 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.[12] In case of agglomerates with PEG, β-CD, EU, GG and XG average diameter was increased than raw crystals but decreased than agglomerates without additives may be due to reduction in the interfacial tension between bridging liquid and crystals and decrease in the adhesive force acting to agglomerate the crystals due to poor adsorption of the additives.[12]

Preparation and evaluation of GLM tablets

It has been observed that tablets from all agglomerates have shown uniform thickness and hardness with improved disintegration time as compared with marketed tablets (Table 2). Also the values of weight variation and friability were within the prescribed limit.[7] It has indicated that GLM direct compressible tablets were successfully prepared from all agglomerates.

***In vitro* dissolution studies**

Rate of dissolution of raw crystals and spherical agglomerates of GLM were shown in Fig. 2. It was observed that for marketed tablets of GLM up to 82% drug was released in 30 min while for tablets with agglomerates of GLM more than 87% drug was released in 20 min except for tablets with PVP agglomerates (73%). The order of drug release was: β-CD > PEG > EU > XG > GG > plane > PVP > marketed tablet. These findings might be attributed to increase in porosity and wettability of GLM agglomerates.

Stability studies

The tablets prepared from agglomerates of GLM did not show any significant change in drug content and in vitro drug release during stability study as given in Table 3. It has indicated that the prepared tablets were adequately stable as per regulatory requirements.[8]

Pharmacokinetic study

The pharmacokinetic parameters of GLM marketed tablet and tablets prepared from agglomerates of GLM were given in Table 4. C_{max} and T_{max} values of tablets prepared form agglomerates were higher than that of marketed tablet indicates improved rate of absorption of GLM in agglomerates which was supported by higher AUC values of the agglomerates. MRT and $t_{1/2}$ of GLM with agglomerates was less indicating rapid elimination of drug from the body as compared with that of pure drug which was well supported by high K_e values. Thus the pharmacokinetic study indicated fast absorption and higher bioavailability of drug from tablets of agglomerates in comparison with marketed tablet. Further, the enhanced bioavailability achieved with spherical agglomeration of GLM may reduce the total dose of drug, beneficial for cost effectiveness and improved patient compliance.

Conclusion

The agglomerates were produced by emulsion solvent diffusion with additives and the directly compressible tablets of glibenclamide were effectively prepared with these agglomerates. Flowability, compressibility and elastic recovery were dramatically improved for all agglomerates except for agglomerates with PVP as compared with raw crystals of GLM, resulting in successful tabletting without capping. It concludes that direct compression of spherical crystallization of GLM with selective additives is a satisfactory method to improve compressibility as well as dissolution and bioavailability of GLM.

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Table 1. Yield, drug content, micrometric properties and solubility study of raw crystals and agglomerates of GLM ($n = 3$)

FC	Yield (%)	Drug content (%)	Diameter (μm) n=100	Angle of repose (°)	Bulk density (g/cc)	Carr's Index (%)	Hausner ratio
A	-	-	14.71 (1.10)	52.23 (0.87)	0.322 (0.02)	32.35 (1.31)	1.42 (0.06)
B	97.02 (2.03)	93.23 (2.04)	159.32 (1.10)	23.14 (0.79)	0.281 (0.01)	15.01 (1.12)	1.18 (0.03)
C	96.14 (1.08)	94.12 (1.12)	148.51 (1.00)	22.23 (0.88)	0.279 (0.04)	14.15 (1.01)	1.16 (0.05)
D	96.23 (1.41)	92.11 (3.25)	153.71 (1.20)	23.23 (0.44)	0.275 (0.03)	14.06 (1.31)	1.16 (0.07)
E	95.09 (2.12)	93.23 (2.47)	141.52 (1.3)	24.13 (0.39)	0.271 (0.06)	15.04 (0.90)	1.17 (0.02)
F	97.14 (2.25)	94.47 (1.46)	143.53 (1.20)	26.12 (0.98)	0.276 (0.05)	14.28 (1.34)	1.16 (0.07)
G	95.53 (1.13)	90.43 (2.63)	147.51 (1.00)	21.21 (0.67)	0.269 (0.04)	18.73 (1.11)	1.23 (0.08)
H	91.09 (3.08)	87.32 (2.36)	16.42 (1.10)	39.23 (0.35)	0.332 (0.07)	31.26 (1.42)	1.45 (0.04)

FC: Formulation Codes; Values in parentheses indicates ± SD

Table 2. Evaluation parameters of MT (marketed tablet) and the tablets prepared from all agglomerates of GLM as B: Plane, C: with PEG, D: with β-CD, E: with EU, F: with GG, G: with XG, H: with PVP

FC	Weight variation (mg)	Thickness (μm)	Hardness (kN)	Friability (%)	Disintegration time (min)
MT	180.34 (± 2.11)	2.81 (± 0.31)	7.34 (± 1.21)	0.234 (± 0.03)	3.23 (± 0.44)
B	100.23 (± 1.52)	2.12 (± 0.12)	8.23 (± 1.32)	0.211 (± 0.05)	2.16 (± 0.62)
C	100.64 (± 1.81)	2.13 (± 0.23)	8.13 (± 1.12)	0.198 (± 0.06)	3.56 (± 0.54)
D	100.27 (± 1.61)	2.11 (± 0.24)	6.53 (± 2.33)	0.324 (± 0.04)	2.25 (± 0.63)
E	100.34 (± 2.14)	2.15 (± 0.12)	7.25 (± 1.12)	0.265 (± 0.08)	2.63 (± 0.51)
F	100.24 (± 1.15)	2.12 (± 0.24)	6.63 (± 2.53)	0.237 (± 0.07)	3.61 (± 0.36)
G	100.16 (± 1.31)	2.13 (± 0.21)	6.21 (± 1.25)	0.287 (± 0.08)	2.83 (± 0.53)
H	100.62 (± 1.52)	2.15 (± 0.19)	7.42 (± 2.16)	0.301 (± 0.06)	3.45 (± 0.65)

Table 3. Stability study data of tablets prepared from spherical agglomerates of GLM of batch B to H

FC	0 day		30 day		60 day		90 day		180 day	
	DC	DR	DC	DR	DC	DR	DC	DR	DC	DR
B	92.12 (2.34)	96.32 (1.43)	91.56 (2.34)	95.72 (1.56)	90.45 (2.56)	94.84 (1.21)	91.45 (1.35)	96.14 (2.14)	90.67 (1.34)	94.93 (3.19)
C	90.32 (1.45)	97.34 (1.34)	90.45 (1.28)	96.83 (1.12)	88.34 (2.62)	96.12 (1.00)	89.35 (1.42)	97.14 (1.00)	88.56 (2.23)	95.95 (2.32)
D	91.23 (3.00)	98.66 (1.41)	90.23 (2.45)	98.43 (1.45)	89.13 (3.43)	97.64 (1.00)	90.23 (1.29)	98.16 (1.00)	88.35 (1.23)	96.83 (2.37)
E	94.45 (2.00)	97.33 (1.23)	92.45 (2.78)	96.36 (1.14)	91.45 (2.63)	96.14 (1.42)	91.15 (1.39)	95.35 (2.43)	90.67 (2.34)	95.17 (1.39)
F	91.67 (1.00)	96.62 (1.35)	90.76 (1.45)	95.84 (1.24)	90.76 (2.20)	95.95 (1.43)	88.67 (1.48)	96.14 (1.13)	89.27 (1.32)	95.33 (1.24)
G	92,92 (2.00)	94.67 (2.34)	90.65 (2.76)	94.13 (2.45)	89.87 (1.56)	92.83 (3.37)	66.56 (2.45)	93.83 (1.84)	89.75 (2.34)	93.07 (1.65)
H	93.45 (2.00)	86.34 (3.89)	92.34 (3.36)	85.32 (2.78)	91.47 (1.25)	83.52 (2.45)	89.67 (2.29)	86.76 (1.37)	88.36 (1.29)	83.15 (2.97)

DC: Drug content (%), DR: Drug release (%), n=3; Values in parentheses indicates ± SD; not significantly different from the values of 0 days as $p > 0.1$ for 30, 60, 90 and 120 days

Table 4. Pharmacokinetic parameters MT (marketed tablet) and the tablets of all agglomerates of GLM as B: Plane, C: with PEG, D: with β-CD, E: with EU, F: with GG, G: with XG, H: with PVP

FC	Parameters					
	C_{max} (ng/ml)	T_{max} (h)	AUC_{0-8} (μg-h ml^{-1})	$t_{1/2}$ (h)	MRT (h)	K_e (h^{-1})
MT	80.74 (9.81)	1.51 (0.05)	78.71 (3.72)	3.41 (0.06)	6.21 (0.07)	0.348 (0.00)
B	110.34 (10.52)*	1.52 (0.04)	96.62 (5.64)**	3.22 (0.07)*	5.43 (0.08)*	0.359 (0.00)
C	116.29 (12.24)*	1.51 (0.09)	108.74 (2.15)**	3.33 (0.05)*	5.63 (0.06)*	0.369 (0.00)
D	122.43 (9.52)*	1.53 (0.07)	110.61 (6.37)**	2.52 (0.06)*	5.42 (0.07)*	0.378 (0.00)
E	118.24 (11.3)*	1.52 (0.08)	116.52 (9.91)**	3.13 (0.05)*	5.67 (0.04)*	0.361 (0.00)
F	116.34 (12.4)*	1.51 (0.06)	112.42 (7.22)**	3.21 (0.04)*	5.81 (0.07)*	0.364 (0.00)
G	115.74 (10.8)*	1.52 (0.04)	109.41 (8.42)**	3.31 (0.05)*	5.82 (0.07)*	0.366 (0.00)
H	110.29 (9.4)*	1.50 (0.03)	101.81 (7.33)**	3.33 (0.08)	5.91 (0.06)	0.354 (0.00)

Significantly different from the value for MT of GLM at $p<0.001$ (**), $p<0.01$ (*). All data in parentheses indicates ± SD, n=6

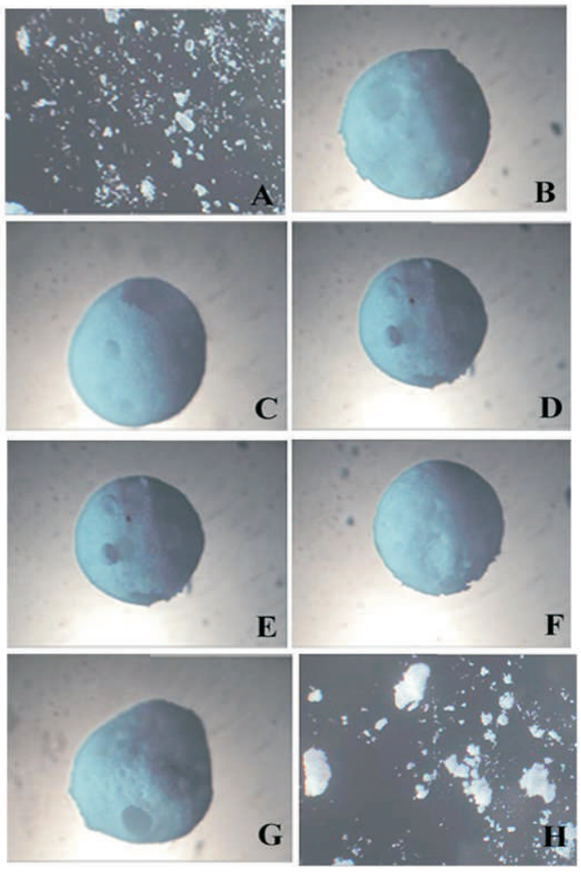

Fig. 1: Microphotographs of GLM and its spherical agglomerates

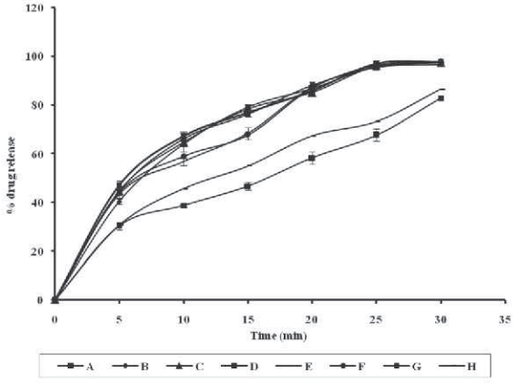

Fig. 2: Dissolution study of marketed GLM tablets (A); and tablets prepared from agglomerates of GLM. Key: B: Plane, C: with PEG, D: with β-CD, E: with EU, F: with GG, G: with XG, H: with PVP

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