Preparation and characterization of spherical agglomerates of gliclazide using novel carrier system

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ABSTRACT

Objective: Gliclazide is well established molecule and widely used for the management of type II diabetes. It exhibits very slight solubility in water, poor flow and compression characteristics. Hence directly compressible gliclazide-disintegrant agglomerates with improved water solubility, flow and compression characteristics for the enhancement of bioavailability

Method: Gliclazide agglomerates were prepared by spherical crystallization technique using a three solvent system comprising acetone: dichloromethane (DCM): water (good solvent, bridging liquid and bad solvent, respectively). Poly vinyl pyrrolidine (PVP) in different concentrations were used as hydrophilic polymer. The effect of speed of rotation and amount of bridging liquid on spherical agglomeration were studied. The agglomerates were

subjected to various physicochemical evaluations such as practical yield, drug content, particle size, porosity, IR spectroscopy, differential scanning calorimeter studies, scanning electron microscopy, micromeritic properties, solubility and dissolution studies.

Results: The agglomerates showed improved micromeritic properties as well as dissolution behaviour in comparison to conventional drug crystals. The optimized agglomerates showed good sphericity as well as high drug release, and hence they were compressed into tablets by direct compression. The tablets were found within the limits with respect to various physicochemical parameters. The dissolution rate of prepared tablets was better than that of marketed tablet and pure drug. The optimized agglomerates and tablet formulations were found to be stable for 3 months under accelerated conditions.

Conclusion: The optimized agglomerates exhibited good solubility, wettability, dissolution rate and other physicochemical properties compared to the pure drug.

Keywords: Gliclazide, spherical agglomerates, solubility, dissolution rate, micromeritic properties.

INTRODUCTION

Direct tableting of pharmaceutical materials is a modern method in tablet manufacturing. Such manufacturing of tablets involve simple mixing and compression of powders, which results in a number of overall benefits including time, cost and energy savings. Direct tableting as a technique has been successfully applied to numerous drugs on the industrial scale. The success of any procedure resulting in mechanical properties for tableting is strongly affected by the micromeritic properties of the crystals used[2]. Compressing a drug directly requires good micromeritic properties, such as flowability, and a good reproducible compressibility. Especially, the flowability of needle-shaped or plated-shaped crystals is very poor and these crystals are difficult to handle[3].

Hence it is necessary to evaluate and manipulate the above said properties. To impart these properties the drugs are subjected to particle design techniques. Spherical crystallization is one the techniques of particle design. The particle size can be enhanced by the help of wet granulation method, dry granulation method, extrusion spheronization and by spherical crystallization methods. Gliclazide is an antidiabetic drug given orally in the treatment of type 2 diabetes mellitus, having low water solubility, poor 8 micromeritic and compressional properties. Thus, the main objective of this study was to prepare the spherical agglomerates

of gliclazide in the presence of hydrophilic polymers to improve the micromeritic properties, solubility and dissolution rate.

MATERIALS AND METHODS

Gliclazide was obtained as a gift sample from Yarrow Chem Product. Ltd, Mumbai, India. The polymer Polyvinyl pyrrolidine and Cross carmellose sodium was purchased from S.D. Fine Chem. Ltd., Mumbai, India. All the chemicals and solvents were purchase from S.D. Fine Chemicals, Mumbai, India and are of analytical grade.

Preparation of spherical agglomerates of Gliclazide

A solution of Gliclazide in acetone was added to a solution of polymer in dichloromethane. Drug was crystallized by adding the drug solution to a 500ml capacity beaker containing 100ml cold distilled water. The mixture was stirred continuously for half an hour using controlled speed stirrer (600 - 1000 rpm) to obtain spherical agglomerates. The agglomerates were separated by filtration and dried at room temperature.

The amount of dichloromethane, speed of agitation and amount of polymer were altered to get a desired property of agglomerates.

Characterization of Spherical Agglomerates

Scanning electron microscopy (SEM): The surface morphology of pure drug and spherical agglomerates of gliclazide were studied by scanning electron microscopy (JEOL, 5400 Japan). The samples were sputter coated with gold before scanning. Scanning electron microscopy (SEM) studied the surface morphology of spherical agglomerates. The photographs showed that the pure drug have smaller crystals and irregular in size and shape, where as the prepared spherical agglomerates have larger in size and nearly spherical in shape due to agglomeration of smaller crystal in the vessel. This spherical shape can improve the flowability of agglomerates

Fourier Transform Infrared spectroscopy (FTIR): The spherical agglomerates of gliclazide was triturate with dried potassium bromide using mortar and pestles, the mixture after grinding in to fine powder was kept uniformly in suitable die and compress by using hydraulic press at high pressure. The pure drug and spherical agglomerates were scanned and recorded in the range of 4000-400 cm by using Infrared spectrophotometer (Brooker, Alfa-T, Germany).

DSC (Differential scanning calorimeter) studies

The DSC of pure drug, pure polymer and prepared agglomerates were conducted using shimagzu 1700 DSC instruments. The mass of empty pan and reference pan were considered for calculation of heat flow. The sample mass varied from 3-10 ± 0.5mg and it was placed in a sealed aluminium pan, the coolant used was liquid nitrogen. The sample was scanned at 10^0C/min from 20^0 C-300^0C.

Micromeritic Properties:

Particle size of pure drug and spherical agglomerate F1and F2 were determined by microscopic method using calibrated stage and eye piece micrometer. The flowability of pure drug and spherical agglomerates was assessed by determination of angle of repose. The angle of repose was assessed by the fixed funnel method, The bulk density was obtained by dividing the weight of sample by the final volume of the sample contains in the cylinder. It is the ratio of total mass of agglomerates to the bulk volume of agglomerates. It is expressed in gm/ml. The tapped density of the pure drug and spherical agglomerates was determined by tapped density Apparatus (Electrolab, India) A simple indication of ease with which a material can be induced to flow is given by application of compressibility index. Hausner's ratio should be calculated from bulk density and tap density values.

Solubility Studies:

Solubility of Gliclazide as well as spherical agglomerates was studied in pH 7.4 Phosphate buffer. The excess quantity of spherical agglomerates was added to glass stopper flask containing 50 ml of medium and stirred at 200 rpm at room temperature for 24 hrs on magnetic stirrer, and then solution was filter using a 0.45 μ membrane filter. Appropriate dilution was made and concentration was determined by Spectrophotometrically (Shimadzu, Japan) at 227nm.

Dissolution studies:

Dissolution rate of pure drug as well as spherical agglomerates were carried using the USP dissolution test apparatus 2 (Electrolab, India) with paddle rotating at 75 rpm 0 in 900 ml dissolution medium (7.4 phosphate buffer) at 37 ±0.5 C. Spherical agglomerates equivalent to 100 mg of Gliclazide were taken and filled in to capsule. The dissolution was carried out for 180 min, the sample (5 ml) was withdrawn at specific time interval and the same volume was replaced to maintain sink condition. The absorbance of solution (after filtering through 0.45 μ membrane filter) was analyzed by UV Spectrophotometer (Shimadzu 1700) at 227 nm.

RESULT AND DISCUSSION

Preparation of Spherical agglomerates:

A solution of Gliclazide in acetone was added to a solution of polymer in dichloromethane. Drug was crystallized by adding the drug solution to a 500ml capacity beaker containing 100ml cold distilled water. The mixture was stirred continuously for half an hour using controlled speed stirrer (600 - 1000 rpm) to obtain spherical agglomerates. The agglomerates were separated by filtration and dried at room temperature. The amount of dichloromethane, speed of agitation and amount of polymer were altered to get a desired property of agglomerates.

Differential Scanning Calorimetry (DSC)

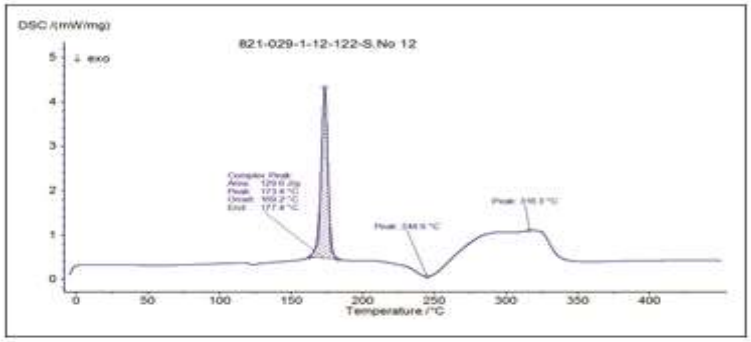
The DSC patterns of pure gliclazide and its crystal forms are shown in Fig.1. Pure gliclazide showed a sharp peak at 173.4 °C corresponding to its melting point. There was a negligible change in the melting peak of the physical mixture and prepared spherical crystals compared to pure drug (170.1 and 17.3°C, respectively). PVP alone did not show any peak in DSC studies. This observation further supports the IR spectroscopy results, which indicated the absence of any interactions between the drug, PVP and additives used in the preparation.

Table No.1 Interpretation of FTIR spectrum of Gliclazide

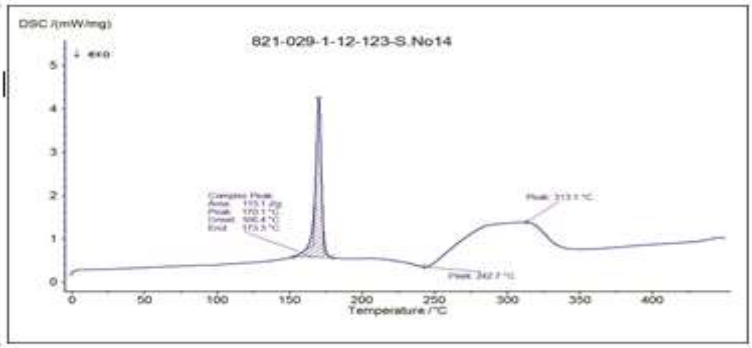
Observed Values Peaks (cm^{-1})	Standard Values Peaks (cm^{-1})	Assignment
1595.83	1500-1600	C=C stretching of an aromatic vibration
3273.81	3300-3500	Amines
2945.97	3000-3100	C-H stretching of an aromatic ring
1438.91	1470-1430	C-H deformations
751.43	800-700	Basic characteristic of aromatic mono-substitution
1162.39	1230-1030	C-N stretching bands of amines
2866.94	2890-2860	C-H stretching vibrations
994.60, 896.39, 1086.81	1300-800	C-C stretching

However, there was a decrease, although very small, in the melting point of the drug in the physical mixture and final spherical crystals compared to that of pure gliclazide this may be increased solubility of drug from the prepared crystals was increased

Fig: No:1 DSC of Pure Gliclazide



DSC of Pure gliclazide



DSC of spherical agglomerates

Fig: No:2 DSC of Spherical Agglomerates

Scanning Electron Microscopy(SEM) :

Scanning electron microscopy (SEM) studied the surface morphology of spherical agglomerates. The photographs showed that the pure drug have smaller crystals and irregular in size and shape, where as the prepared spherical agglomerates have larger in size and nearly spherical in shape due to agglomeration of smaller crystal in the vessel. This spherical shape can improve the flowability of agglomerates

Fig: No:3 Scanning Electron Microscopy of Pure Gliclazzide

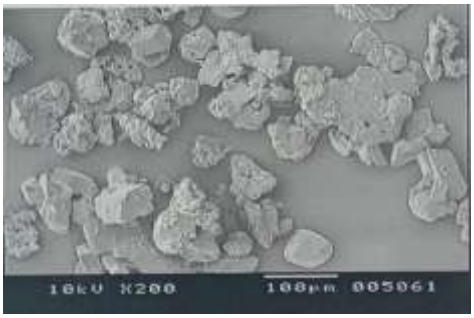


Fig: No:4 Scanning Electron Microscopy of Spherical Agglomerates at 600 rpm

Fig: No:5 Scanning Electron Microscopy of Spherical Agglomerates at 800 rpm

Fig: No:6 Scanning Electron Microscopy of Spherical Agglomerates at 100 rpm

Fourier Transform Infrared Spectroscopy

The principal IR peaks of pure gliclazide, physical mixture and spherical crystals are shown in Table no.01 IR spectra of gliclazide showed characteristic peaks. There were no considerable changes in the IR peaks of the physical mixture and spherical crystals when compared to pure gliclazide. If there is any strong interaction between drug and carrier, it often leads to identifiable changes in the IR profile and melting point of the drug. The results of IR spectra indicated the absence of any well-defined interaction between gliclazide and PVP in the presence of acetone, DCM and water. This was further supported by DSC results.

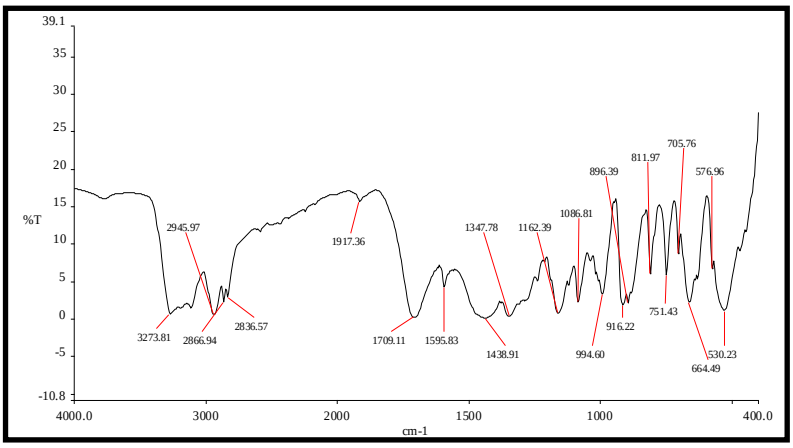


Fig: No:7 FTIR Spectra of Gliclazide

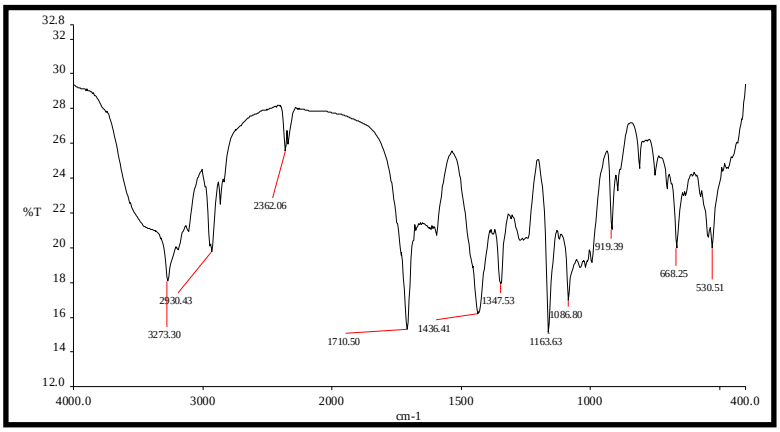


Fig: No:8 FTIR Spectra of spherical agglomerates

Micromeritic properties of agglomerates

The results of loose bulk density (LBD) and tapped bulk density (TBD) are presented in Table No.2. These parameters were used to assess the packability of the crystals. The pure drug powder was more bulky and fluffy, which was indicated by the lowest LBD value (0.39 ± 0.005 g mL–1, *n* = 3). The highest TBD value (0.58 ± 0.015 g mL–1, *n* = 3) of pure drug indicates a high intergranular space between particles. In contrast, the spherical agglomerates exhibited higher LBD (0.29 ± 0.02 to 0.33 ± 0.01 g mL–1, *n* = 3) and TBD (0.43 ± 0.02 to 0.49 ± 0.01 g mL–1, *n* = 3) values. These results indicate good packability of the prepared spherical crystals when compared with pure gliclazide.

The results of Carr's index, Hausner's ratio and angle of repose of spherical crystals in comparison with pure drug are presented in Table No: 2. These parameters were used to assess the flow and compressibility properties of the agglomerates. Carr's index and Hausner's ratio of pure drug were 30.00 ± 1.88% and 1.42 ± 0.041 (*n* = 3), respectively, indicating extremely poor flow properties. The powder could not pass through the funnel

during the angle of repose experiment. The poor flow of gliclazide could be due to the irregular shape and high fineness of the powder, which posed hurdles in the uniform flow from the funnel. On the other hand, all the prepared crystals exhibited low Carr's index, Hausner's ratio and angle of repose values, indicating excellent flow properties and compressibility (Carr's index: 7.38 ± 2.32 to 13.78 ± 1.61%, *n* = 3; Hausner's ratio: 1.06 ± 0.01 to 1.18 ± 0.02, *n* =3; angle of repose: 19.79 ± 1.75 to 28.36 ± 1.43°, *n* = 3). The improved flowability and compressibility of spherical agglomerates may be due to the sphericity, regular and larger size of crystals. Among all the prepared spherical crystals, the agglomerates prepared with PVP exhibited good micromeritic properties.

Table No.2: Micromeritic properties of spherical agglomerates formulated with PVP

Formulation	% Yield	ρ_b (g/ml)	ρ_t (g/ml)	Carr's index	Hausner's Ratio	Angle of repose(^{o})	Particle Size (μm)
F1	87.33	0.31	0.49	13.78	1.18	28.36	677.3.±37.52
F2	81.81	0.30	0.45	9.99	1.06	19.79	471.0±23.52
F3	80.66	0.29	0.44	10.15	1.07	26.15	249.4±29.06
F4	81.81	0.30	0.45	9.99	1.06	19.79	471.0±23.52
F5	86.29	0.32	0.44	7.38	1.15	21.66	571.0±23.52
F6	84.71	0.32	0.46	11.35	1.13	25.68	563.0±18.03
F7	81.81	0.30	0.45	9.99	1.06	19.79	471.0±23.52

Particle size and size distribution

The mean particle diameter of agglomerates is shown in Table No.2. The pure drug exhibited a very small particle size (40.97 ± 2.25 mm, *n* = 3) whereas the size of prepared agglomerates was found between 249.4 ± 29.06 to 677.3 ± 37.52 mm, *n* = 3, which is significantly different from that of pure drug. There was uniformity in batch-to-batch with respect to the size range of crystals. The size of the crystals increased with an increase in the PVP concentration. The shape of the crystals, when observed using an optical microscope, was spherical in all the prepared crystal formulations.

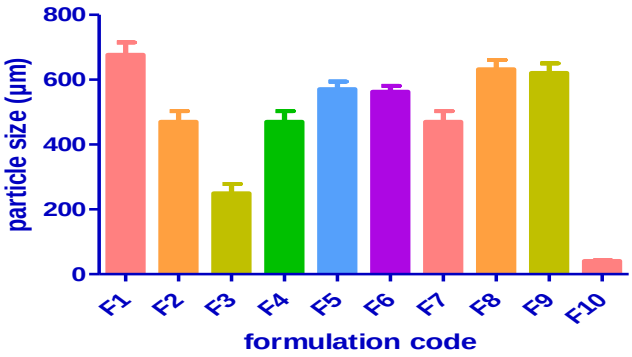


Fig: No:9 Average particle size of gliclazide spherical agglomerates

In vitro dissolution studies

The results of in vitro dissolution studies are shown in Fig.10 and Table No.3. Pure gliclazide exhibited less release at the end of 180 min in phosphate buffer 7.4 (20.46 ± 0.2%, *n* = 3); spherical crystals improved the dissolution rate of gliclazide in phosphate buffer 7.4 as dissolution medium (increase from 43.84 ± 3.14 to 74.12 ± 4.36 compared to that of pure drug). The dissolution rate was increased with an increase in DCM concentration. Among the formulations prepared, F-6 (with 2 ml DCM) showed highest drug release in 3 h. These results clearly reveal that the dissolution rate of gliclazide was increased in the form of spherical agglomerates when compared to its pure form. This may be due to increase in concentration of DCM for the preparation of spherical agglomerates of gliclazide.

Table No.3 In vitro dissolution data for spherical agglomerates at the end of 180 minute

Time in min										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
15	0.57	12.92	0.96	12.92	5.85	0.34	12.92	0.71	0.65	7.05
30	1.45	21.69	2.08	21.69	19.86	1.23	21.69	1.19	1.19	7.74
45	3.88	31.14	4.17	31.14	31.09	2.62	31.14	2.0	2.73	11.24
60	5.88	37.50	21.10	37.50	38.88	19.34	37.50	9.46	11.46	13.04
90	10.58	44.37	28.72	44.37	46.0	35.60	44.37	20.30	20.56	15.75
120	31.07	49.38	39.59	49.38	50.55	57.95	49.38	37.8	42.34	17.69
150	36.50	52.98	46.95	52.98	52.48	69.93	52.98	44.67	48.04	19.26
180	43.84	54.93	50.69	54.93	54.43	74.12	54.93	49.68	54.03	20.46

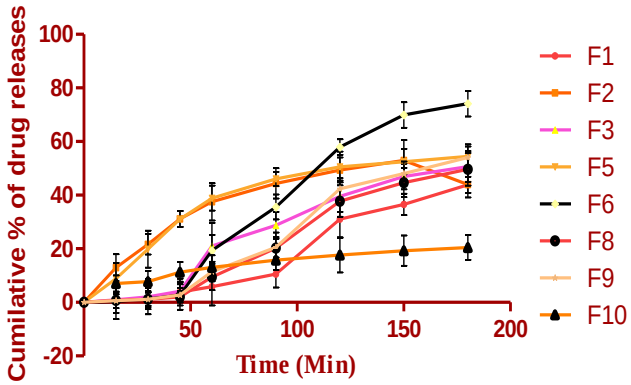


Fig: No:10 : Dissolution profile of pure drug and agglomerates in PB pH 7.4

Solubility profile:

The solubility profile of pure gliclazide indicated the drug was freely soluble in organic solvent and practically insoluble in water. The result of glicazide solubility in water and 7.4 phosphate buffer was shown in the below table.

Table No.4. Solubility profile of gliclazide in various solvents

Sl No	Formulation	Pure Drug	SD Value
1	Solubility in water in %	5.15	0.001
2	Solubility in 7.4 phosphate buffer in %	19.42	0.014

From the saturation solubility of drug was found to be 5.15% mg/ml in distilled water and 19.42% in phosphate buffer 7.4.

CONCLUSION

Gliclazide-disintegrant agglomerates were successfully prepared for direct tableting by use of a spherical agglomeration technique. The solubility and micromeritics of the agglomerates, such as flowability, packability and compatibility were dramatically improved, resulting in successful direct tabletting without capping. The main factor in the improvement of the flowability and packability was a significant reduction in interparticle friction, due to the spherical shape of the tableted particles. Compatibility of the agglomerates was much

improved. The dissolution rate of gliclazide from the gliclazide-disintegrant agglomerates was enhanced significantly with increasing the amount of disintegrant.

In conclusion, the present study demonstrated the successful preparation of spherical agglomerates and directly compressible tablets of gliclazide. If this process can be scaled-up to manufacturing level, this technique has the potential to develop into an invaluable technology in future.

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Conflict Of Interest

There is no conflict of interest from all the authors.

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