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Preparation and Characterization of Spherical Agglomerates of Gliclazide

Londhe S.R*, Thenge R.R, Mahajan N.M and Adhao V.S

Department of Pharmaceutics, IBSS College of Pharmacy, Malkapur - 443101, Maharashtra, India

ABSTRACT

Gliclazide, an antidiabetic drug, exhibit poor water solubility and micromeritic properties. Thus the aim of present study was to improve the dissolution rate and micromeritic properties of gliclazide by spherical agglomeration method in the presence of hydrophilic polymer such as PVP K30 and PEG 4000. Crystallization medium for the spherical agglomerates of gliclazide consist of ethanol (good solvent), water (poor solvent) and chloroform (bridging liquid) in the ratio of 20:65:15 mL. The prepared spherical agglomerates were evaluated for micromeritic properties, solubility, dissolution rate and compare with pure drug. Also agglomerates were characterized by Scanning electron microscopy, Infrared Spectroscopy, Differential scanning calorimetry and X-ray Diffractometry. The spherical agglomerate showed improved in the micromeritic properties compare to pure drug. The four fold increased in the solubility and thus increased the dissolution rate of spherical agglomerates than that of pure drug.The agglomerate posses nearly spherical shape and smooth surface. The Infrared spectroscopy indicate that there is no significant interaction between the drug and polymer.The data of DSC showed that there is slight changes in the melting point of spherical agglomerates.The XRD spectra indicate the decrease in the crystallinity of agglomerates. This could be due to polymorphic changes in the spherical agglomerates.

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Keywords: Spherical agglomeration, Gliclazide, Solubility, Dissolution rate, Micromeritic Properties.

INTRODUCTION

Direct tableting is economical, facilitates processing without need of moisture, heat and small numbers of processing steps are involved.[1] For direct tableting it is necessary to increase flow ability and compressibility of bulk powder in order to retain steady supply of powder mixture to the tableting machine. Because direct tableting necessities an active ingredient powder that excels in flowability, bindability, mechanical strength and other qualities more than the materials for indirect tableting. There are currently limited pharmaceutical tablets on commercial production that can be made by direct tableting. For that reason development of the design method of active ingredient, agglomerates that can be directly tableted has been waited.[2]

Yoshiski Kawashima and co-workers developed the technique spherical crystallization, a novel agglomeration technique that can transform directly the fine agglomerates produced in the crystallization or in the reaction process into a spherical shape.[3] Spherical crystallization is a nonconventional particle size enlargement technique that involves crystallization and agglomeration using bridging liquid. Use of bridging liquid improves compressibility by acting as granulating fluid. This technique improves both the process ability such as mixing, filling, tableting, characteristics and the bioavailability of pharmaceuticals.[4] Size enlargement processes to upgrade fine particulates are assuming ever-increasing importance today, because it is a multiple unit process in which crystallization, agglomeration and spheronization can be carried out simultaneously in one step. The resultant agglomerates can be designated as spherical agglomerates.[5,6] Due to the improved characteristics of agglomerates, the micromeritic properties such as flow ability, packability and compressibility of the resultant agglomerates are dramatically improved, so that direct tableting or coating is possible without further processing (mixing, agglomeration, sieving etc).[7] One of the prominent features of the spherical agglomeration process is versatility in controlling the type and size of the agglomerates.

Gliclazide is an antidiabetic drug given orally in the treatment of type 2 diabetes mellitus, having low water solubility, poor micromeritic and compressional properties. [8] Thus the main objective of this study was to prepare the spherical agglomerates of gliclazide in the presence of hydrophilic polymer such as PEG 4000 and PVP K30 to improve the micromeritic properties, solubility and dissolution rate.

MATERIALS AND METHODS

Gliclazide was obtained as a gift sample from Atra pharmaceutical Pvt. Limited, Aurangabad, India. The polymer PEG4000 and PVP K30 was purchased from Molychem. Limited, 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:

Gliclazide (1.5g) was dissolved in 20 ml of ethanol (good

***Address for Correspondence:**

Mr. S.R.Londhe, Department of Pharmaceutics, IBSS College of Pharmacy, Malkapur-443101, Maharashtra, India.

E-mail: rajuthenge11@gmail.com

solvent) heated at 40^{0}C until clear solution was obtained. The drug solution was poured quickly in to 65 ml solution containing 5 % of PVP K30 (poor solvent). After 10 min the drug was crystallized, the whole system was thermally controlled at 6^{0}C. and the stirring was continued at a speed of 800 rpm (Remi, India).When fine crystals of gliclazide with PVP K30 begin to precipitates, the chloroform (15 ml) was added dropwise. After 30 min. stirring, the spherical agglomerates were formed. The agglomerates were separated by filtration using whatman filter paper no.1 and were dried at room temperature for 24 hrs. The agglomerates were kept in desiccators for further studies.

The above same procedure was carried out for the preparation of spherical agglomerates of gliclazide in the presence of PEG 4000 (5 %).

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.

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^{-1} by using Infrared spectrophotometer (Brooker, Alfa-T, Germany).

Differential scanning calorimetry (DSC):

After calibration, thermo grams were obtained by heating all the samples (5 mg) of pure drug and its spherical agglomerates at a constant heating rate of 10^{0}C/min with chart speed of 40 ml/min under an atmosphere of nitrogen. The exact peak temperatures, melting point and heat of fusion were determined. The temperature range for the scan was 30^{0}C to 300^{0}C for all the samples.

Powder X-ray diffraction (PXRD):

X-ray diffraction pattern of pure drug and spherical agglomerates of gliclazide were obtained using the X-ray diffractometer (BRUKER D8 ADVANCE, Germany) at 40 kV, 30 mA and a scanning rate of 0.02^0 /min at the diffraction angle 2θ over the range of 10-80^0 using Cu (as anode) radiation of wavelength 1.5406 Å.

Micromeritic Properties:

Particle size of pure drug and spherical agglomerate $F_1$and F_2 were detemined by microscopic method using calibtrated 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 0.1*N* HCL. 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 Whatmann filter paper. 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 50 rpm in 900 ml dissolution medium (0.1 N HCL) at 37 ±0.5^{0}C. Spherical agglomerates equivalent to 30 mg of Gliclazide were taken and filled in to capsule. The dissolution was carried out for 60 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 Whatman filter) was analyzed by UV Spectrophotometer (Shimadzu, Japan) at 227 nm.

RESULT AND DISCUSSION

Preparation of Spherical agglomerates:

Solvent change method is used to prepare spherical agglomerates of gliclazide. The three phase solvent system was used, consists of Ethanol (good solvent), distilled water (bad solvent) and chloroform (bridging liquid). Different compositions of solvents were tried and best one was selected on the basis of formation of spherical agglomerates in the vessel. Gliclazide was first dissolved in ethanol (good solvent) at 40^{0}C then resultant solution was poured in to poor solvent (hydrophilic polymer solution (5%, PEG 4000) and 5% PVP K30. The addition of bridging liquid promotes the transfer of drug to third emulsified phase in which agglomerates grow spherically. several parameter were consider, the necessary requirement in spherical

crystallization is the bridging liquid should be immiscible with hydrophilic polymeric solution and drug should slightly soluble in bridging liquid with reference to above fact toluene and chloroform tried as bridging liquid. Toluene resulted in formation of clumps instead of spherical agglomerates this could be due to over solubilization of the drug but when chloroform was used as bridging liquid spherical agglomerates were formed hence it was selected as bridging liquid. Amount of bridging liquid is critical parameter in spherical crystallization process, when less amount of chloroform was used no agglomeration occurred which was due to fact that very little amount of bridging liquid was available for solubilization. Addition whole amount of bridging liquid at a time resulted of localization of bridging liquid hence poor agglomerates formed. Drop wise addition of bridging liquid resulted in spherical agglomerates. Excellent spherical agglomerates produce when agitation at 800 rpm.

Chraterization of spherical agglomerates :

Scanning Electron Microscopy(SEM) :

Scanning electron microscopy (SEM) studied the surface morphology of spherical agglomerates Shown in Fig.1 (a-d) . 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.

Differential scaning calirometery (DSC) :

DSC studies were carried for pure drug and spherical agglomerates of gliclazide shown in Fig. 2. The DSC thermogram of pure drug shows endrothermic peak at 170.81 corresponding to its melting points, where as the DSC thermogram of spherical agglomerates formulation F_1 and

Fig1. (a): SEM of pure drug

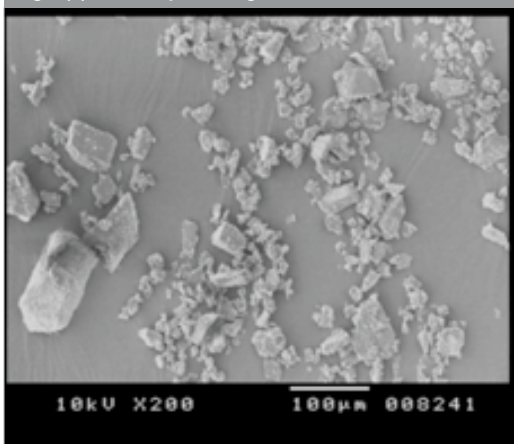


Fig1. (b): SEM of spherical agglomerate F_1

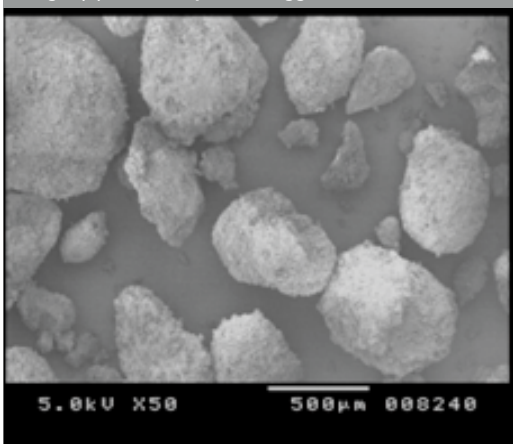


Fig.1 (c): SEM of spherical agglomerate F_2

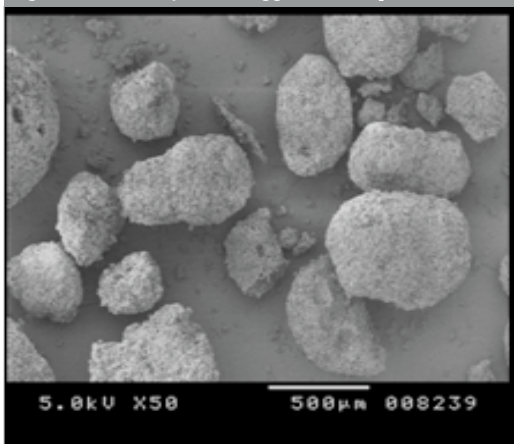
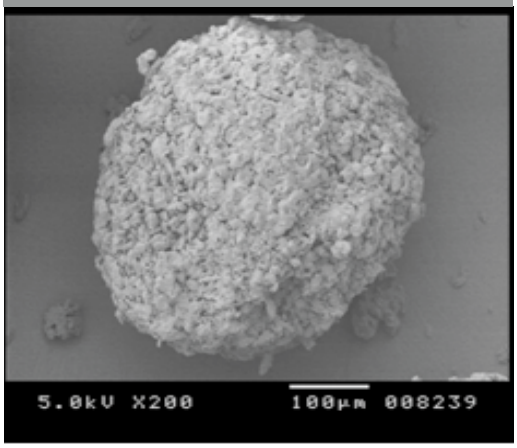


Fig.1 (d): SEM of spherical agglomerate at 200X



F_2)showed the endothermic peak at 167.79 and 166.80 corresponding to its melting point respectively. These DSC data showed that there is slight changes in the melting point of spherical agglomerates compare to pure drug. The decrease in the melting point may be due to decrease in crystallanity of of spherical agglomerates.

Infrared Spectroscopy (FTIR) :

FTIR spectra of pure drug and spherical agglomerate was shown in Fig 3. FTIR studies were carried out to check wheather there is any changes in the pure drug after spherical crystallization. FTIR spectra of pure drug and spherical agglomerates when compare, it shows near same characteristic peaks indicate that there is no significant changes occured in the pure drug after spherical crystallization. This confirmed that there is no significant interactions between the drug and polymer. All the peak values are shown in Table No-1.

Micromeritic Properties :

The micromeritic properties of pure drug and spherical agglomerates were shown in Table 2.

Particle size of pure drug and spherical agglomerate $F_1$and F_2 was detemined by microscopic method using calibtrated

Fig. 2:DSC Spectra of Pure dug (A) , spherical agglomerate F_1 (B) and spherical agglomerate F_2(C)

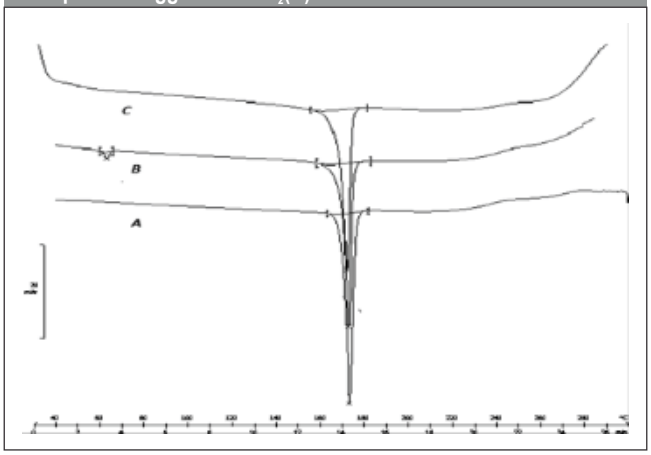


Table 1: FTIR data of pure drug and spherical agglomerates

Formulation	N-H stretching	C-H stretching	C=O stretching	S=O stretching	C=C stretching
Pure Drug	3273.62	2949.94	1710.05	1349.65	1596.40
F_1	3273.45	2949.76	1710.07	1348.55	1596.31
F_2	3273.61	2932.37	1710.16	1348.66	1595.22

Fig. 3 : FTIR Spectra of Pure dug (A),spherical agglomerates F_1(B) and spherical agglomerates F_2(C)

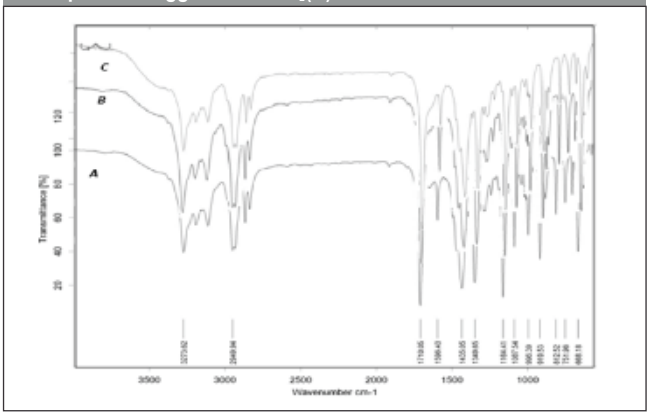
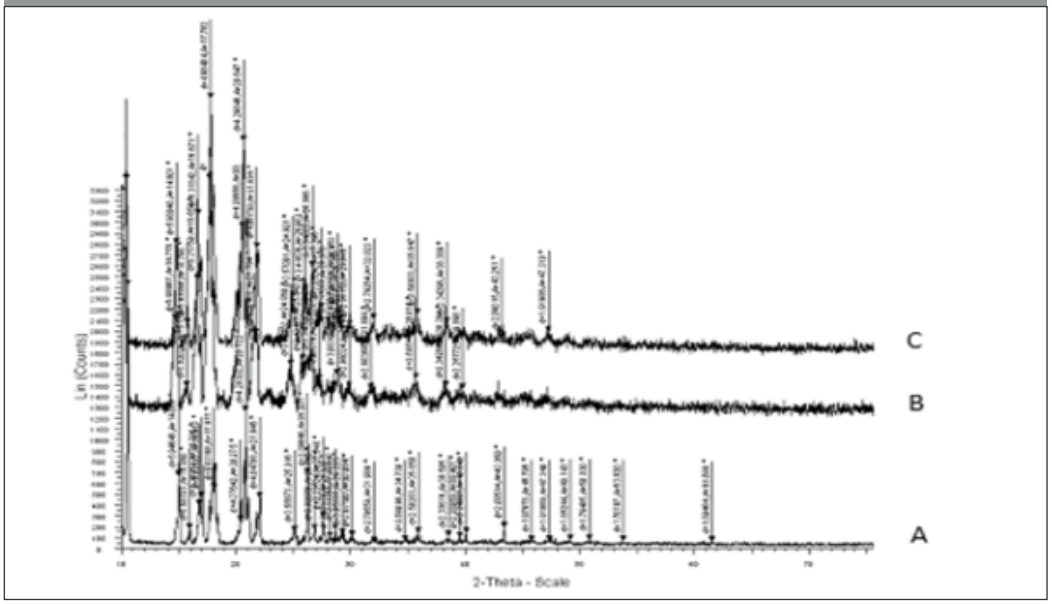


Fig. 4:XRD Spectra of Pure dug (A), spherical agglomerate F_1(B) and spherical agglomerate F_2(C).



stage and eye piece micrometer. The particle size of pure sample is small (53.62±0,041µm) compare to spherical agglomerates ($F_1$374.08±0.41µm and F_2–402.05±0.43µm). Bulk density and tapped density of pure drug and spherical agglomerates was determine by tapped density appratus. The pure drug having low bulk density and tapped density values (0.61±0.32 and 0.93±0.006g/ml) indicate that the pure drug is pluffy and irregular crystal. Due to this the packaging of crystal are not uniform where as the bulk density and tapped density of formulation F_1 and F_2 have (0.94±0.013, 1.10±0.008g/ml) and (0.96±0.04 and1.11±0.009 g/ml) respectively indicate that the agglomerates have good packagbility. The flow properties of pure drug and spherical agglomerates were studied by fixed funnel method. The pure drug having the angle of repose (43.70^0±1.82) which indicate the poor flow properties due to smaller, irregular shape and size of crystals, where as the spherical agglomerates F_1 and F_2 showed (28.9^0±0.31) and (29.7^0±0.34) angle of repose respectively indicate the better flow properties due to larger and spherical size of agglomerates. This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction due to their spherical shape and lower statics electric charge.

Solubility study:

Solubility of pure drug and Spherical agglomerate F_1 and F_2were studied in 0.1 *N* HCL shown in Table 2. The solubility of spherical agglomerate F_1 and F_2 was significantly improved compare to pure drug in 0.1 *N* HCL.This is due to increase in wettability of drug in the presence of hydrophilic polymer (PVP K 30, PEG 4000).

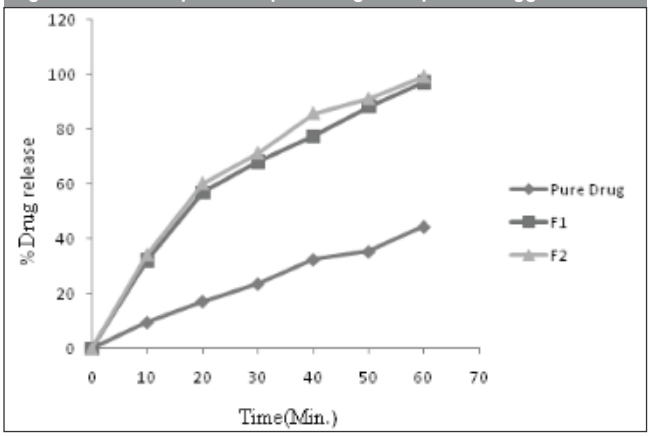
Table 2: Micrometric Properties of pure drug and its spherical agglomerate

Properties	Formulation		
	Pure Drug	F1	F2
Drug Content (%)	----	99.18±1.22	98.36±1.35
Paricle size (µm)	53.62±0.041	374.08±0.41	402.05±0.43
Carr's Index(%)	34.40±0.053	14.54±0.13	13.51±0.15
Bulk density (g/cm^3)	0.61±0.32	0.94±0.013	0.96±0.04
Tapped density (g/cm^3)	0.93±0.006	1.10±0.008	1.11±0.009
Hausner´s ratio	1.52±1.0	1.17±1.0	1.15±1.0
Angle of repose(°)	43.70±1.82	28.9±0.31	29.7±0.34
Solubility (mg/ml)	0.81±0.03	3.18±0.02	3.36±0.02

Dissolution study :

Dissolution studies of pure drug and spherical agglomerates of gliclazide was carried out in USP dissolution appratus and shown in Fig. 5. The percentage drug release of pure drug in 0.1 *N* HCL was found to be (44.53%) within 60 min. where as dissolution rate of spherical agglomerates obtained in the presence of PVP K 30 and PEG 4000 was found to be (97.26, 99.21%) respectively at the end of 60 min. This increase in the dissolution rate of spherical agglomerates could be due to the wetting of drug in the presence of hydrophlic polymer.

Fig. 5:Dissolution profile of pure Drug and spherical agglomerates.



CONCLUSION

Spherical agglomerates of gliclazide were successfully prepared by spherical crystallization method. The micromeritic properties such as flowability, packability and compactibility of agglomerates were significantly improved compared to pure drug. Enhancement of solubility and dissolution rate of agglomerates was due to incorporation of hydrophilic polymer such as PVP K30 and PEG-4000. The FTIR, DSC, XRD study also revealed that there was no change in the crystal structure during spherical crystallization. Thus spherical crystallization can successfully employed to obtained spherical agglomerates of gliclazide for direct tableting.

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