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Spherical crystallization of glipizide for improvement of micrometric properties

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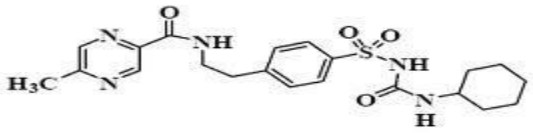
Abstract

Glipizide is an anti diabetic drug with water insolubility and poor compressibility. Glipizide pure drug was converted into spherical crystal agglomerates via the spherical crystallization technique using dichloromethane-water-chloroform solvent system. The various parameters optimized were type, amount and mode of addition of bridging liquid, temperature and agitation speed to get maximum amount of spherical crystals. These were characterized for micromeritic properties (particle size and shape, flow ability), pack ability (bulk density), wet ability (contact angle) and compressibility. It was revealed from the study that spherical agglomerates exhibited improved flow ability, wet ability and compaction behavior.

Keywords: Speherical Crystallization, Glipizide, Micrometric Properties.

Introduction



Glipizide

One of the most revolutionary technologies in the manufacture of solid dosage forms is tableting by direct compression. It is economical, facilitates processing without the need for moisture and heat and only few procedures are involved. In the direct compression method it is necessary to increase the flow ability and compressibility of the bulk powder in order to have sufficient mechanical strength of the compacted tablets[1]. More recently, a modified crystalline technique has been adopted for the development of directly compressible drugs. This technique, also known as spherical crystallization, is a particle engineering technique by which crystallization and agglomeration can be carried out simultaneously in one step to transform crystals directly into a compacted spherical form[2]. This technique as the name indicates, provides crystalline agglomerates that are spherical in shape, which exhibit excellent micromeritic properties of many drugs such as Fenbufen[3], ibuprofen[4], furosemide[5], indomethacin[6], aminophylline[7], enoxacin[8], tolbutamide[9, 10], sulphamethoxazole[11], phenytoin[12] and norfloxacin[13]. There are four methods for preparing spherical crystals. These are; (i) Simple spherical crystallization, (ii) emulsion solvent diffusion, (iii) ammonia diffusion, and (iv) neutralization[14]. The aim of present work was spherical crystallization of glipizide. Glipizide is an oral hypoglycemic agent, which is a commonly prescribed drug for the treatment of patients with type II diabetes [15]. It is used adjunct to diet to the management of type II (non-insulin dependent) diabetes mellitus in patients whose hyperglycemia cannot be controlled by diet and exercise alone. Glipizide stimulates insulin secretion from the β∟ cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. Glipizide is a weak acid (pKa = 5.9) practically insoluble in water and acidic environment and highly permeable (class II) drugs according to the Biopharmaceutical Classification System (BCS)[16].

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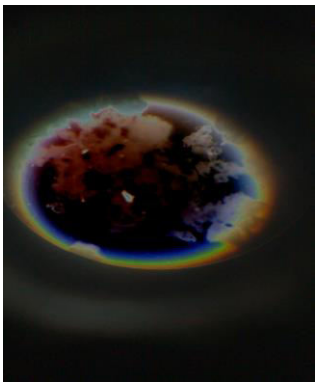
In the present work spherical crystals of glipizide (SC of glipizide) were prepared by simple spherical crystallization and various in vitro parameters of these have been evaluated. Simple spherical crystallization process is easy, common and faster relative to other methods and hence this process was chosen for the preparation of spherical crystals.

Material and methods

All reagents used in this investigation were of analytical grade and double distilled water was used. The Glipizide (100 mg) was dissolved in dichloromethane (3 ml) in a small beaker. Distilled water (10 ml) was added to precipitate the drug in fine crystals. The mixture was allowed to stand for 10 minutes. It was then stirred using three blade electric stirrers at 500 to 600 rpm and chloroform (0.5 ml) was added drop wise as a bridging liquid while stirring. This system was agitated for 45 minutes at room temperature. Spherical crystals were separated by filtration and dried in oven at 40^0C[17-18].

Results and Conclusion

The effect of various parameters was investigated in order to achieve optimal conditions for spherical crystallization of Glipizide. The effect of type of bridging liquid on formulation of SC of Glipizide was determined by using benzene, chloroform and toluene. The effect of the volume (0.1 to 0.5 ml) of bridging liquid (chloroform) on the formation SC of Glipizide was investigated. The other parameters evaluated were agitation speed (300, 600 and 900), room temperature (RT) and drop-wise addition of bridging liquid. The effect of different temperatures on the formulation of SC of Glipizide was investigated at room temperature (RT) and 50 ± 1^0. The other parameters kept constant i.e. amount of bridging liquid (0.5ml), agitation speed (600 rpm) and drop wise addition of bridging liquid (chloroform). The effect of rate of addition of bridging liquid on formulation of SC of Glipizide was also determined. The parameters maintained constant were, type of bridging liquid (chloroform), amount of bridging liquid (0.5 ml), agitation speed (600 rpm) and temperature (RT). The in vitro pharmaceutical and physicochemical attributes of the optimized formulation (SC of Glipizide) and Glipizide were evaluated. Particle shape was determined using optical microscopy. **Fig. Spherical Crystals of Glipizide**



Bulk density was determined using a graduated measuring cylinder. Tapped density was determined by tapping cylinder at 100 times and % compressibility was determined by calculating ratio between tapped density and bulk density. Flow ability was determined in terms of angle of repose (fixed funnel method). A known amount of each formulation (Glipizide and SC of Glipizide) was allowed to drop on a graph paper placed on the smooth surface of a tile. Height and diameter of pile of powder were recorded[17].

Amount of bridging liquid is a critical process parameter in spherical crystallization process. Five batches were prepared. When 0.1 ml chloroform was used no agglomeration occurred, which was due to the fact that very little amount of bridging liquid was available for solubillization necessary for agglomeration. When 0.3 ml of chloroform was used partial agglomeration occurred. A volume of 0.5 ml of chloroform resulted in the form of good crystals with free flowing properties. Addition of whole amount of bridging liquid at a time, resulted in localization of bridging liquid and hence formation of poor spherical crystals. Drop wise addition of bridging liquid and resulted in efficient agglomeration. Excellent spherical crystals were produced when agitated at 500 to 600 rpm. With increasing agitation speed, crystals with randomly broken edges were obtained, which was due to high shear force of blades of agitator. Under agitation speeds slower than 250 rpm, the resultant agglomerates became more irregular and some of them adhered to shaft and vessel wall.

No agglomeration occurred on lowering the temperature of solvent water mixture to 4 ± 2^0 even on prolonged mixing. This was possibly due to decreased solubility of the drug in the agglomeration solvent at such a lower temperature. Less solubilization of the drug would cause reduced wetting (and hence thickness) of the drug particles, and therefore, decreased agglomeration. In another batch, large agglomerates were formed on raising the temperature to 50 ± 2^0, which could be due to the increased solubility of the drug at this temperature.

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Glipizide crystals were found to have higher angle of repose in comparison to SC of Glipizide, which could be due to the irregular shape of these crystals that is reflected from fig. 1, which hindered in the uniform flow of crystals from funnel. The reason for excellent flow ability of spherical crystals is the perfect spherical shape and larger size of crystals (Table 2). Spherical crystallization is a potential approach to the manufacture of spherical agglomerates and these exhibit excellent micromeritic properties for direct tableting. In this study, spherical agglomerates of Glipizide showed increased micromeritic properties, which may be helpful to increase the dissolution rate of poorly soluble tableting by direct compression due to augmented flow properties and compaction behaviour. Utilizing spherical crystallization technique as the last step during bulk drug production can improve the efficiency of manufacturing tablets.

Table 1: Effects of various parameters on formation of spherical crystals of Glipizide

Parameters		**Observation**
Type of bridging liquid	Benzene	Clump
	Toluene	Clump
	Chloroform	Spherical crystals
Amount of bridging liquid (ml)	0.1	No agglomeration
	0.3	Partial agglomeration
	0.5	Spherical crystals
Agitation speed (rpm)	300	Irregular crystals
	600	Spherical crystals
	900	Small agglomerates
Temperature	Room temperature	Spherical crystals
	$>50^0$C	Large agglomerates
Mode of addition of bridging liquid	Whole amount	Irregular crystals
	Drop wise	Spherical crystals

Table 2: In-vitro characterization of formulations of Glipizide and spherical crystals of Glipizide

S. No.	**Parameters**	**Formulation**	
		Glipizide	**SC of drug**
1.	Compressibility (%)	24.46	14.28
2.	Bulk density (gm./cm^3)	0.71	0.96
3.	Tapped density (gm./cm^3)	0.94	1.12
4.	Hausner ratio	1.32	1.16
5.	Angle of repose (Degree)	46.7	29.8

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