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Original research

Improvement of the dissolution behavior of gliclazide, a slightly soluble drug, using solid dispersions

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ABSTRACT

Gliclazide is a second generation sulphonylurea used in the treatment of type 2 diabetes characterized by a low risk of hypoglycaemia and cardiovascular disorders. This drug shows poor water solubility, particularly at low pH values, that may cause reduced and variable absorption after oral administration, above all in fasted state. To improve gliclazide dissolution behavior, different drug carrier systems were prepared and tested using two different methods: co-mixing and co-milling. The samples produced were characterized by differential scanning calorimetry, powder X-ray diffraction, and scanning electron microscopy. Their dissolution rate was tested and compared to an immediate release commercial product. Several approaches were effective for a rapid and complete dissolution of this drug: co-milling with suitable hydrophilic carriers such as cross-linked swellable polymers or amorphous silica and co-milling with a small amount of sodium lauryl sulphate (10 mg). In the case of the highest dose (80 mg) both approaches should be used at the same time to avoid saturation of the medium.

1. Introduction

Type 2 diabetes mellitus, is a chronic metabolic disease characterized by insufficient insulin secretion by pancreatic β-cell and/or diminished tissue responses to insulin; it is the most common form of diabetes mellitus, accounting for approximately 90% of cases. An uncontrolled diabetes leads to several long-term complications which include cardiovascular disorders, retinopathy, nephropathy and peripheral neuropathy [2]. Currently, in addition to lifestyle modification, which remains the cornerstone of management of type 2 diabetes mellitus, metformin is the first-line oral therapy. However its use is associated to several side effects like nausea, vomiting, diarrhea, abdominal pain (that occur in approximately 20% of patients) and rarely to serious lactic acidosis [18], [20]. Sulphonylureas are an alternative for patients with contraindication to metformin [8]. Gliclazide is a second generation sulphonylurea that is used in the treatment of patients with type 2 diabetes because it has similar efficacy compared to other sulphonylureas, but a lower risk of hypoglycaemia and cardiovascular disorders since it has a selective inhibitory activity towards pancreatic ATP-sensitive potassium (KATP) channels and a shorter half-life compared to others sulphonylureas [19]. Moreover it has unique antioxidant properties and other beneficial haemobiological effects [23]. Gliclazide is available as oral tablets, 30 and 80 mg strength. This hypoglycemic agent is formulated both as immediate release and as modified release formulation; the severity of glycemia will determine the dosage and the kind of formulation, requiring adjustment to obtain the optimal response at the lowest dosage. Gliclazide is an example of class II Biopharmaceutical Classification System (BCS) compound, its oral bioavailability depends on the drug dissolution rate and solubility in the gastrointestinal tract. Gliclazide shows poor water solubility (55 μg/ml) [1] and dissolution properties and this can give rise to low and erratic bioavailability and poor dose-effect proportionality [11]. Moreover being gliclazide a weak acid (pKa 5.8) [22] its solubility is lower in acid medium and this could be a problem in the design of an immediate release oral dosage form because the entire dose should be promptly released in very short times in the upper part of the gastrointestinal tract. Therefore, the improvement of gliclazide dissolution behavior is an important issue for enhancing its bioavailability and therapeutic efficacy. Different methods have

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been proposed to improve the solubility and/or the dissolution rate of poorly soluble drugs such as micronization [17], salt formation [5], co-crystals [6], complexation [16] and solid dispersions [7,10,24] [21]. demonstrated an increase in gliclazide dissolution rate, compared to gliclazide suspension and gliclazide alone, using ordered binary and ternary mixture of the drug with water soluble excipients. A significant enhancement of gliclazide dissolution rate was also obtained using solid dispersion prepared with silica and polyvinypyrrolidone K30 [12], polyvinylpyrrolydone K90 [4] and PEG 6000 [3]. Several mechanisms were suggested for the improvement of the dissolution properties of insoluble drugs from solid dispersions, including particle size reduction of the drug, complete or partial transformation to the amorphous state, reduction of aggregation and improved drug wettability [7]; [10]. Conventional methods for solid dispersion preparation include solvent evaporation, melt crystallization, hot-melt extrusion, lyophilization; these methods are efficient, but they are characterized by several disadvantages [26]; [27]. In the melting method, water-soluble polymers which can solve drugs are limited, and the high process temperatures may adversely affect drug stability. Solvent evaporation methods have recently attracted considerable attention, although they require organic solvents and are quite expensive processes [28]. Powders co-mixing and co-grinding is an alternative solid dispersion generating method. Many authors have demonstrated the efficacy of the co-grinding method for the enhancement of the dissolution rate of various poorly soluble drugs such as danazolo, felodipine [29], nateglinide [13], aclofenac [15]. Co-grinding is an environmentally friendly and solvent-free method, it avoids the thermal degradation of the drugs, it does not require sophisticated equipments, it is industrially feasible and can be easily scaled-up. In this work, to enhance the dissolution behavior of gliclazide, some solid dispersions were prepared, in different drug to polymer ratios. The dissolution behavior of the co-ground systems was evaluated and compared to that of the corresponding physical mixtures and to some commercial gliclazide formulations, considered as references. Solid state characterization of drug-carrier systems was carried out by scanning electron microscopy (SEM), differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD) to investigate possible drug modifications.

2. Materials and methods

2.1. Materials

Gliclazide was kindly donated by Labochim S.p.A. (Milan, Italy); crosslinked polyvinylpyrrolidone (PVPC) Polyplasdone® XL-10 was from GAF corporation (New York, USA); sodium starch glycolate (SSG) Primojel® from Elko (Milan, Italy); crosslinked carboxymethyl cellulose (CMCC) Ac-Di-Sol® from FMC Europe (Brussel, Belgium); amorphous silica (AS) (Syloid® 72FP) from Grace Davison (Milan, Italy); mannitol (M) (Pearlitol® 200SD) from Roquette-Italy (Cassano Spinola, Italy); polyoxyethylene polyoxypropylene tri-block copolymer Poloxamer (PO) (Kolliphor P 407 Micro) from BASF (Ludwingshafe, Germany). All the chemicals were of reagent grade, and all the materials were used as received. Some dosage forms available on the Italian market were also evaluated. Two immediate release (IR) formulations were Diabrezide® (80 mg gliclazide; Merck Serono S.p.A., Rome, Italy), gliclazide EG® (80 mg gliclazide; EG S.p.A., Milan, Italy). Five modified release (MR) formulations were: Diamicron® (30 mg gliclazide; Servier Italia S.p.A., Rome, Italy) Dramion® (30 mg gliclazide; I.F.B. Stroder S.r.l., Florence, Italy), gliclazide EG® (30 mg gliclazide; EG S.p.A., Milan, Italy), gliclazide Mylan generics (gliclazide 30 mg; Mylan S.p.A., Milan, Italy).

2.2. Methods

The particle size analysis was determined, by laser diffraction, Coulter LS 230 (CoulterCorp., Miami, FL, USA), on raw gliclazide and on a drug sample treated alone in the same conditions used for the production of the drug-carrier co-milled systems, to verify a possible particle size reduction.

Gliclazide solubility was determined in triplicate in over saturation conditions by dispersing an excess of drug in volumetric flasks at 21 °C in distilled water. The suspensions were left under constant magnetic stirring, 300 rpm, for 24 h. At 2, 4, 6 and 24 h, an aliquot of the liquid was filtered through a Millipore membrane (pore size 0.45 μm), properly diluted and the drug concentration

Table 1
$T_{50\%}$ ± Standard Deviations (S.D.) of gliclazide alone, gliclazide treated (T) and physical mixtures (PM) or co-milled (CM) drug-carrier systems in distilled water or HCl 0.1 N (*).

Dose	Drug carrier system	Method	Code	$T_{50\%}$ (min) ± S.D.
30 mg	Gliclazide	–	GLI	45 ± 6.3
	Gliclazide treated	T	GLI T	160 ± 32
	Gliclazide: Mannitol 1:8	PM	GLI:M 1:8	>60
	Gliclazide: Amorphous Silica 1:8	PM	GLI:AS 1:8	18 ± 6.3
	Gliclazide: Crosslinked Polyvinyl Pyrrolidone 1:8	PM	GLI:PVPC 1:8	17.3 ± 0.57
	Gliclazide: Mannitol 1:8	CM	CM GLI:M 1:8	17 ± 7.4
	Gliclazide: Amorphous Silica 1:8	CM	CM GLI:AS 1:8	7.6 ± 1.5
	Gliclazide: Crosslinked Polyvinyl Pyrrolidone 1:4	CM	CM GLI:PVPC 1:4	13 ± 6.7
	Gliclazide: Crosslinked Polyvinyl Pyrrolidone 1:6	CM	CM GLI:PVPC 1:6	6.2 ± 1.1
	Gliclazide: Crosslinked Polyvinyl Pyrrolidone 1:8	CM	CM GLI:PVPC 1:8	4.6 ± 0.52
	Gliclazide: Crosslinked Carbossy Methyl Cellulose 1:8	CM	CM GLI:CMCC 1:8	5.8 ± 0.96
	Gliclazide: Sodium Starch Glycolate 1:8	CM	CM GLI:SSG1:8	12 ± 0.78
	Gliclazide:Sodium Lauryl Sulphate	CM	CM GLI:SLS	2.2 ± 0.25
80 mg	Gliclazide	–	GLI	>60
	Gliclazide: Mannitol 1:8	CM	CM GLI:M 1:8	36 ± 10
	Gliclazide: Amorphous Silica 1:8	CM	CM GLI:AS 1:8	7.3 ± 1.7
	Gliclazide: Crosslinked Polyvinyl Pyrrolidone 1:8	CM	CM GLI:PVPC 1:8	11 ± 0.28
	Gliclazide: Sodium Lauryl Sulphate	CM	CM GLI:SLS	3.7 ± 0.57
	Gliclazide: Sodium Lauryl Sulphate: Crosslinked PolyvinylPyrrolidone 1:4	CM	CM GLI:SLS:PVPC 1:4	13 ± 2.9
	Gliclazide: Sodium Lauryl Sulphate: Crosslinked PolyvinylPyrrolidone 1:8	CM	CM GLI:SLS:PVPC 1:8	14 ± 2.4
	DIABREZIDE®	–		35 ± 2.1
	Gliclazide: Sodium Lauryl Sulphate: Crosslinked PolyvinylPyrrolidone 1:4	CM	CM GLI:SLS:PVPC 1:4	5.8 ± 3.7*
	Gliclazide: Sodium Lauryl Sulphate: Crosslinked PolyvinylPyrrolidone 1:8	CM	CM GLI:SLS:PVPC 1:8	5.9 ± 0.82*
	DIABREZIDE®	–		47 ± 4.5*