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Molecular interaction between glimepiride and Soluplus®-PEG 4000 hybrid based solid dispersions: Characterisation and anti-diabetic studies

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ABSTRACT

The objective of this study was to evaluate a novel blend of polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol 6000 grafted copolymer (Soluplus®) and polyethylene glycol (PEG) 4000 for solubility enhancement, physicochemical stability and anti-diabetic efficacy of the produced solid dispersions containing glimepiride, a biopharmaceutics classification system (BCS) class II sulphonylurea. Different batches of glimepiride solid dispersions (SD) were prepared by the solvent evaporation method using the individual polymers and blends of the polymers at different ratios. The Soluplus®-PEG 4000 (sol-PEG) hybrid polymer based glimepiride solid dispersions were characterized by differential scanning calorimetry (DSC), fourier transform infrared (FTIR) spectroscopy, micromeritics and dissolution studies. In vivo anti-diabetic activity was determined by measuring the changes in blood glucose concentrations in albino rats. The solid dispersions showed good flow properties and excellent practical yield. Drug content and release from the different formulations increased when Soluplus® was used as the main matrix polymer. The kinetics of drug release from all the solid dispersions followed first order. Solid state characterization confirmed the formation of amorphous glimepiride solid dispersions in the Sol-PEG hybrid polymer and no strong drug–polymer interaction was observed. The blood glucose reduction in albino rats by the Sol-PEG-Glim SDs was significantly ($p < 0.05$) higher and more sustained when compared with the plain drug sample and commercially available product. Optimized SD batches (SP1 and SP3) showed a reduction in blood glucose level from 100% to 9.81% and 8.97%, respectively, at T_{max} of 3 h. The Sol-PEG-Glim SD was found to be stable over a period of 6 months (at 40 °C, 70% RH) with no significant changes in the drug content. Thus, the Sol-PEG polymeric hybrids represent a promising tool for enhanced delivery of glimepiride.

1. Introduction

Diabetes mellitus is the commonest endocrine-metabolic disorder characterized by chronic hyperglycaemia giving rise to the risk of microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischaemic heart disease, stroke and peripheral vascular disease) damages, with associated reduced life expectancy and diminished quality of life (Heydari et al., 2010). Diabetes is a huge and growing global problem with high and escalating cost to the society. It is a major cause of morbidity and mortality, worldwide (Knowler et al., 2002; Wild et al., 2004). In every six seconds a person dies from diabetes and 76% of diabetes related deaths are in people under the age of 60 (International Diabetes Federation (IDF) diabetes atlas, 2014).

According to the International Diabetes Federation (IDF) diabetes atlas 2014 update, about 352 million people are living with diabetes which is projected to increase by 55% by 2035 especially from the number of people with type II diabetes. In Africa, about 22 million people are living with the disorder with a prevalence of 5.1%. This number is proposed to increase by 109% by 2035. This region also has the highest percentage of people living with the disorder but yet undiagnosed. Nigeria, among other countries in Africa, accounts for the highest number of people living with diabetes. (International Diabetes Federation (IDF)

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diabetes atlas update, 2014). These data on the prevalence and epidemiology is undesirable for a disorder which has different conventional drugs for its management.

Sulphonylurea, especially the third generation agents are a major therapeutic agent used for treatment. Glimepiride is one of the third generation sulphonylurea antidiabetic drugs which stimulate insulin secretion. It is used in treatment of non-insulin dependent diabetes mellitus (NIDDM or type II diabetes) (Du et al., 2013). According to biopharmaceutical classification system, it belongs to the class II drugs. These drugs exhibit poor solubility and high permeability. In addition, glimepiride shows a low pH dependent solubility (Dixit et al., 2012; Bhasin, 2014). In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37 °C (<0.004 mg/ml). In a medium pH > 7, solubility of the drug is slightly increased to 0.02 mg/ml (Dixit et al., 2012; Bhasin, 2014). The poor aqueous solubility and slow dissolution rate of glimepiride poses some difficulties in its dosage design, leads to unpredictable bioavailability, irreproducible clinical response or therapeutic failure in some cases due to low therapeutic plasma drug levels (Li et al., 2015). This would result in grave implications like development of complications in the long run.

Nevertheless, the use of glimepiride in management diabetes has been hindered due to its associated undersirable side effects which can be reduced through administration of low doses, utilising formulation strategies which enhance its delivery (Aloisio et al., 2013).

Several formulation techniques have been adopted to solve the dissolution and/or solubility associated with drugs namely, the use of prodrugs (Beaulieu et al., 2015), complexation methods with cyclodextrin (di Cagno et al., 2014; Lin et al., 2014), micronisation and crystal technology (Gouthami et al., 2015), nanotechnology (Liu et al., 2014; Junyaprasert and Morakul, 2015), etc. However, these approaches have their drawbacks ranging from failure to form active forms in vivo, laborious methods of preparation, formation of agglomerates, toxicity issues, etc. (Sameer et al., 2011; Luo et al., 2014; Fu et al., 2014).

Solid dispersion via the use of biodegradable polymers not only overcomes some of the limitations of previous approaches but it is also a virtually feasible method to enhance bioavailability of poorly water-soluble drugs including glimepiride (Meng et al., 2015). It combines the benefit of solubilisation and maximizing the surface area of the drug. Several methods are conventionally used to prepare solid dispersions namely fusion method (ArunPrasad et al., 2010), kneading method (Santos Alves et al., 2014), hot-melt extrusion (Djuris et al., 2013; Hanpin and Hoag, 2013), use of supercritical fluids (SCF) (Yang et al., 2015), co-grinding method (Guo et al., 2014) etc. with some disadvantages of thermal degradation and instability of the drug, aggregation of particles etc. which limits their use. Solvent evaporation method is a widely used technique to prepare solid dispersions and is most useful for drugs with high melting point and low therapeutic dose (Yadav and Tanwar, 2015).

Furthermore, various surfactants, polymers, non-polymeric agents etc. have been used singly or in combination as solubilizers to form solid dispersions. However, most of these have limited solubilisation capability and/or inability to form solid solutions (Hauss, 2007; Hardung et al., 2010). Soluplus®-a polyethylene glycol- polyvinyl caprolactam acetate grafted copolymer is a novel thermoplastic internally plasticized amphiphilic polymer particularly made for use in formulating solid dispersions. It has the potential of forming solid solutions with numerous drugs that are poorly water soluble, hence enhancing their dissolution (BASF Technical, 2010; Homayouni et al., 2014; Lust et al., 2015). Based on the nature of carrier, Soluplus® is classified as a fourth generation solid dispersion polymer. It is not only a matrix former but also solubilises the drug dispersed in its matrix. It is amorphous in nature, possesses low glass transition temperature, excellent thermal stability, low toxicity and low bulk density with superior flowability (Guth et al., 2011; Homayouni et al., 2014). It demonstrates excellent solubilisation properties for BCS class II and IV drugs (Fule and Amin, 2014). The exploration of Soluplus®-PEG 4000 polymer hybrids in the development of an effective delivery system for glimepiride, in order to maximize efficacy, reduce the drug's adverse effects and control the progression of diabetes, informs the objective of this study. The objective of this study therefore, is to formulate and characterise solid dispersions (SDs) based on Soluplus®-PEG 4000 hybrid polymers for enhanced delivery of glimepiride.

2. Material and methods

2.1. Materials

The pure sample of glimepiride used was a generous gift by May & Baker Pharmaceutical Ltd. (Lagos, Nigeria). Soluplus® (polyvinyl-caprolactam–polyvinyl acetate–polyethylene glycol grafted copolymer) was kindly provided by BASF (Ludwigshafen, Germany). Other materials include polyethylene glycol (PEG) 4000 (Carl Roth, Germany), alloxan monohydrate (Sigma–Aldrich, Hamburg, Germany), methanol and dichloromethane (Sigma–Aldrich,

Table 1
Formulation composition of solid dispersions, their percentage yields and drug content at 0, 3 and 6 months.

Batch code	Formulation type	Ratio of polymer used (Sol: PEG)	Solvent used	Percentage (%) yield	Initial (DC) (%)	DC (%) in 3 months	DC(%) in 6 months
S_1	Glim:Sol	01:00	Methanol and dichloromethane	96.23	80.71	79.89	79.01
S_2	Glim:Sol	01:00	Methanol	97.82	73.38	72.5	70.88
P_1	Glim:PEG	00:01	Methanol and dichloromethane	97.36	81.1	78.5	78.02
P_2	Glim:PEG	00:01	Methanol	97.44	72.2	69.22	68.97
SP_1	Glim:PEG: Sol	01:01	Methanol and dichloromethane	95.66	88.8	87.09	86.73
SP_2	Glim:PEG:Sol	01:02	Methanol and dichloromethane	97.66	85.5	84.17	83.85
SP_3	Glim:PEG: Sol	01:05	Methanol and dichloromethane	96	86.6	85	84.69
SP_4	Glim:PEG:Sol	05:01	Methanol and dichloromethane	97.23	78.8	76.8	76.51
SP_5	Glim:PEG:Sol	01:01	Methanol	97.24	76.6	74.03	74

Key: Glim—Glimepiride, Sol—Soluplus®, PEG—Polyethylene glycol 4000, DC—drug content.

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