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# Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique

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**Abstract**

Solid dispersions (SDs) of glibenclamide (GBM); a poorly water-soluble drug and polyglycolized glycerides (Gelucire®) with the aid of silicon dioxide (Aerosil® 200); as an adsorbent, were prepared by spray drying technique. SDs and spray dried GBM in comparison with pure GBM and corresponding physical mixtures (PMs) were initially characterized and then subjected to ageing study up to 3 months. Initial characterization of SDs and spray dried GBM by DSC and XRPD showed that GBM was present in its amorphous form (AGBM). Improvement in the solubility and dissolution rate was observed for all samples. DRIFT spectroscopy revealed presence of hydrogen bonding in SDs. During ageing study, almost no decrease of in vitro drug dissolution was observed, over the period of 3 months as compare with freshly prepared SDs. Slight crystallinity in SDs was observed in the DSC and XRPD studies during ageing. Moreover in vivo study in Swiss Albino mice also justified the improvement in the therapeutic efficacy of amorphous GBM in SDs over pure GBM. Thus, present study demonstrated the high potential of spray drying technique for obtaining stable free flowing SDs of poorly water-soluble drugs using polyglycolized glycerides carriers with the aid of silicon dioxide as an adsorbent.


*Keywords:* Solid dispersions; Amorphous; Polyglycolized glycerides; Silicon dioxide; Spray drying

## 1. Introduction

Spray dried solid dispersions (SDs) were widely studied recently as an option to improve dissolution rate and in turn bioavailability of poorly water-soluble drugs (particularly BCS class II drugs) (Serajuddin, 1999). Though SDs suffers from thermodynamic instability, use of anti-plasticizing agents, and improvement of $T_g$ by using polymers like polyvinylpyrrolidone (PVP) has shown promising results (Paradkar et al., 2004). But use of higher amounts of these polymers in the SDs has resulted problems in the design of formulations such as tablets, like failure of tablet disintegration, sticking to punches etc. Also the solvent required to dissolve drug and excipients increases significantly with increase in the excipients amount, which may affect process economy. For example, complete conversion of crystalline curcumin to its amorphous form was reported to occur at 1:7 (w/w) ratio of curcumin:PVP with high amount of the solvent (around 8.5% (w/v) solution in warm ethanol) required for processing (Paradkar et al., 2004). High amount of hydrophilic polymer may also increase the availability of

*Abbreviations:* AGBM, amorphous form of GBM; DRIFTS, diffuse reflectance infrared fourier transform spectroscopy; DSC, differential scanning calorimetry; GBM, glibenclamide; PEG, polyethylene glycols; PMs, physical mixtures; PM GBM:A, physical mixtures of GBM and Aerosil; PM GBM:A:50/13, physical mixtures of GBM + Aerosil + Gelucire 50/13; PM GBM:A:44/14, physical mixtures of GBM + Aerosil + Gelucire 44/14; Polyglycolized glycerides, Gelucire®; PVP, polyvinylpyrrolidone; SDs, solid dispersions, SD GBM:Asolid dispersion of GBM and Aerosil; SD GBM:A:50/13, solid dispersion of GBM + Aerosil + Gelucire 50/13; SD GBM:A:44/14, solid dispersion of GBM + Aerosil + Gelucire 44/14; SEM, scanning electron microscopy; Silicon dioxide, Aerosil 200®; TGA, thermal gravimetrical analysis; XRPD, X-ray powder diffraction

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the moisture, which may aid to divitrification. Use of low melting point excipients like polyethylene glycols (PEG) and polyglycolized glycerides have been used widely as excipients in SDs. These excipients have shown to cause faster drug dissolution by improving wettability of the drug particles, significant reduction in particle size during the formation of SDs or the inherently higher rate of dissolution of the soluble component of SDs, which would pull along the more insoluble but finely mixed drug into the dissolution medium (Dordunoo et al., 1991; Leuner and Dressman, 2000; Passerini et al., 2002). The polyglycolized glycol esters like Gelucires® are reported to reduce erratic bioavailability of poorly water-soluble drugs (Pozzi et al., 1991). However, previous report showed that PEG has not been effective in transforming loperamide into its amorphous form (Weuts et al., 2005). Similarly stickiness is imparted by these low melting point excipients cause processing problems. Silicon dioxide (Aerosil® 200) is one of the important carriers due to the presence of surface silanol groups; may be able to form hydrogen bonds with drug molecules during formulation of SDs, which cause faster drug dissolution by improving wettability of the drug particles. There are two types of silica, porous and nonporous. Several grades of silica particles having different properties, such as particle size, degree of hydrophilicity and hydrophobicity, and pore structure, are available for both types. Aerosil® 200 is a nonporous hydrophilic form of silica. It was also confirmed that the drug was molecularly dispersed in the matrix formed with silica particles (Morefield, 2000; Watanabe et al., 2002).

Glibenclamide (GBM) is a second-generation orally administered sulphonylurea derivative with potent hypoglycemic activity (Davis and Granner, 1996). GBM shows poor solubility in gastrointestinal fluids, which can give rise to variations in its dissolution rate and incomplete and/or unpredictable bioavailability. Recently, many workers reported the enhancement of dissolution rate of GBM by preparation of SDs using polyglycolized glycerides (Gelucire®) by fusion methods (Tashtouch et al., 2004; Galal et al., 2003). But amount of lipid required in the formulation was significantly high. Preparation of SDs by conventional spray drying technique using polyglycolized glycerides carriers has been problematic. The sticky and tacky mass of polyglycolized glycerides is produced by conventional spray drying technique. Taking into consideration these problems the use of polymers and lipids in the spray dried SDs; attempt has been made to stabilize the spray dried amorphous drug with low amount of polyglycolized glycerides in combination with silicon dioxide as an adsorbent.

In the present study, SDs of GBM with polyglycolized glycerides (Gelucire 50/13 and Gelucire 44/14) in combination with silicon dioxide were attempted by spray drying method. The SDs were characterized in comparison with pure drug and corresponding physical mixtures (PMs) in the same ratios using drug content, thermal gravimetrical analysis (TGA), scanning electron microscopy (SEM), diffuse reflectance infrared fourier transform spectroscopy (DRIFTS), differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and in vitro drug release. SDs were further subjected to ageing at 30 °C/65% RH for 3 months and checked for in vitro drug release along with the presence of crystallinity using DSC and XRPD. In addition, improvement in the rate and extent of in vitro drug dissolution from SDs were justified by in vivo study in Swiss Albino mice.

## 2. Materials and methods

### 2.1. Materials

GBM was a generous gift from Sun Pharmaceutical Industries Ltd., (Mumbai, India). Gelucire 50/13 (Stearoyl Macrogoglycerides EP, solid pastilles, nominal mp = 47–50 °C, HLB = 13) and Gelucire 44/14 (Lauroyl Macrogoglycerides EP, semi solid, nominal mp = 38–44 °C, HLB = 14) were generous gift from Gattefossé s.a. (St. Priest, Cedex, France). Aerosil® 200 was supplied by Get-Rid Pharmaceuticals Ltd. (Pune, India). All other chemicals and solvents were of analytical grade.

### 2.2. Preparation of SDs and PMs

GBM either alone or in combination with Gelucire 50/13 or Gelucire 44/14 (1:1 parts by weight) was dissolved in sufficient amount of dichloromethane to obtain 14.5% (w/v) solutions. To these clear solutions silicon dioxide (one parts by weight of GBM was slowly added to obtain uniform suspensions. Spray drying of these suspensions were carried out using laboratory scale spray dryer (Jay Instruments & Systems Pvt. Ltd., Mumbai, India) under following set of conditions: inlet temperature, 38–40 °C; outlet temperature, 26–28 °C; feed rate, 4–6 ml/min; atomization air pressure, 2 kg/cm$^2$ and aspiration, −250 mmWC. PMs in the same ratios were also prepared by physically mixing drug and excipients thoroughly for 10 min in a mortar until a homogeneous mixture was obtained. All the samples were passed through fine mesh (150 μm) and stored in desiccated environment until further study. The SDs and PMs were denotes as SD GBM:A, solid dispersion of GBM and Aerosil; SD GBM:A:50/13, solid dispersion of GBM + Aerosil + Gelucire 50/13; SD GBM:A:44/14, solid dispersion of GBM + Aerosil + Gelucire 44/14; PM GBM:A, physical mixtures of GBM and Aerosil; PM GBM:A:50/13, physical mixtures of GBM + Aerosil + Gelucire 50/13; PM GBM:A:44/14, physical mixtures of GBM + Aerosil + Gelucire 44/14.

### 2.3. Drug content

SDs equivalent to 5 mg of GBM were weighed accurately and dissolved in suitable quantity of methanol. The drug