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Application of Plackett–Burman screening design for preparing glibenclamide nanoparticles for dissolution enhancement

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ABSTRACT

This study is to improve the dissolution characteristics of a poorly water-soluble drug glibenclamide (GLB), by preparing nanoparticles through liquid anti solvent precipitation. A Plackett–Burman screening design was employed to screen the significant formulation and process variables. A total of 12 experiments were generated by Minitab® 16 for screening 5 independent variables namely the amount of poloxamer 188 (PX) (X1), amount of PVP S 630 D (PD) (X2), solvent to antisolvent volume ratio (S/AS) (X3), amount of GLB (X4) and speed of mixing (X5). Mean particle size (Y1), saturation solubility (Y2) and % dissolution efficiency ($\%DE_{5min}$) (Y3) were selected as response variables. All the regression models yielded a good fit with high determination coefficient and F value. The Pareto chart depicted that all the independent variables except the amount of GLB had a significant effect ($p<0.001$) on the response variables. The mathematical model for mean particle size (PS) generated from the regression analysis was given by $PS = 830 - 8.14\ PX + 12.8\ PD - 11.1\ S/AS + 1.42\ GLB\ Conc. - 0.676$ speed of mixing ($R^2 = 93.5$, $F_{ratio} = 17.28$, $p<0.001$). Prepared GLB nanoparticles exemplified a significant improvement ($p<0.05$) in the release as compared to pure GLB with the optimum formulation releasing almost 80% drug within first 5 min. The X-ray diffraction studies concluded that the crystallinity of nanoparticles from the optimum batch was intact and the increased dissolution could be ascribed to conversion of unmilled GLB to nanoparticles.

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1. Introduction

According to the food and drug administration nanoparticulate drug is not a generic drug rather is considered as "newdrug" molecule and is not bioequivalent to its microcrystalline or solubilized form administered at the same dose and therefore it can be patented [1]. Nanosuspensions are liquid dispersion consisting of solid drug nanoparticles, stabilized by polymer and/or surfactant offering, fewer side effects, lower doses and faster onset of action [2]. Extensive review has been done on the various approaches for the development and characterization of nanoparticles, nevertheless briefly it has been classified into two basic approaches i.e. top down technology and bottom up technology. The top down approach relies on mechanical attrition to render large crystalline particles into nanocrystals and their reduced size and increased surface area lead to an increased dissolution rate which may offer an increased bioavailability [3]. However, breaking large crystalline drug particles to nanoparticles with size below 100 nm is extremely difficult with these methods since these methods are very time consuming and require significant energy, which might generate a large amount of amorphous particles, and contamination from milling media or homogenization chamber [4]. The bottom up technology involving solvent antisolvent precipitation technique requires dissolving the drug in a solvent which is then added to a non-solvent to precipitate the crystals and the subsequent growth of crystal is controlled by the addition of polymer and/or surfactant to produce fine particles [5]. These methods give better control over particle properties such as, size, morphology and crystallinity as compared to top-down methods [6]. Other solvent removal methods such as, evaporative precipitation into aqueous solution (EPAS) [7] and microemulsions have also been reported, though these are one-step processes they have certain disadvantages such as low yield, degradation of heat sensitive materials, etc. [8]. The supercritical fluid technology is another extensively researched bottom-up technology for the preparation of nanoparticles [9], however, it has inherent disadvantages of using extremely high pressures which require high pressure pumps, temperatures, and specially designed fine nozzles which may pose operational problems.

Glibenclamide [GLB (5-chloro-N-(2-(4-(cyclohexylcarbamoyl)amino sulfonyl)phenyl)ethyl)-2-methoxybenzamide] in Fig. 1, is a potent sulfonylurea and has established potential benefits such as lower dose, rapid onset, lower insulin levels and less-pronounced glucagonotropic effects, insulin-sensitizing and insulin-mimetic affects. However it is a poorly soluble drug (<8 μg/ml in pH 7.4 phosphate buffer) [10] with relatively high permeability through CaCo-2 cell monolayer's which warrants it to be classified under BCS Class II classification [11]. Otoom et al.

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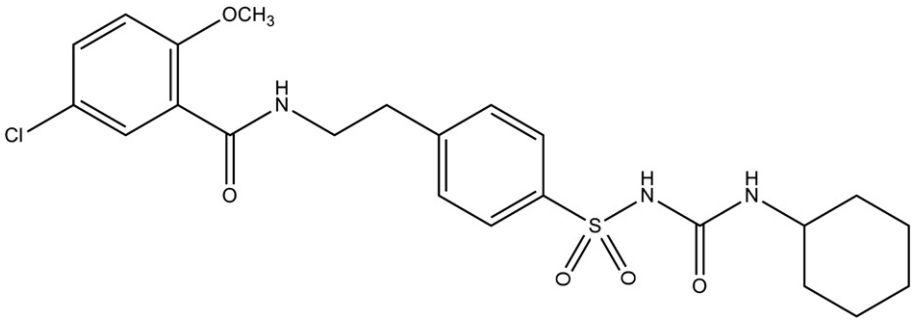

Fig. 1. Glibenclamide.

concluded that GLB administration under fasting condition significantly increases the area under curve for 24 h and increases the maximum concentration of GLB in blood compared to its administration under feeding condition, moreover the lag time was significantly reduced in fasting condition compared to feeding condition suggesting that GLB is effectively absorbed from the gastrointestinal tract, but the presence of food, and certain dietary supplements interfere with its dissolution and in turn its absorption [12]. In view of the time required to reach an optimal concentration in plasma, GLB may be more effective if given 30 min prior to meal [13]. Conversely, this might reduce patient compliance since after taking the drug if the patient is not able to have the meal it would result in severe hypoglycemia and if taken with meal, food would interfere sequentially with its absorption. Hence, improving the dissolution characteristics of GLB might allow its concomitant dosing with food. Various researchers have tried to improve the dissolution characteristics of GLB, but the application of nanotechnology drug delivery for improving the dissolution characteristics of GLB is still in the early hours. Recently Patravale and Bachhav prepared a self microemulsifying drug delivery system (SMEDDS) to improve the GLB dissolution characteristics but concluded that GLB gets degraded in the prepared SMEDDS [14], more recently Singh et al. prepared a self nanoemulsifying drug delivery system (SNEDDS) of GLB and improved its dissolution characteristics [15], however the excessive use of surfactants to dissolve the drug may limit the application of the SNEDDS. Singh et al. also prepared and optimized a nanosuspension formulation using GLB as a model drug [16]. However, a detailed investigation into the preparation of GLB nanoparticles for dissolution enhancement was lacking. In view of all these, the present investigation was aimed to develop, characterize and optimize GLB nanoparticles, to improve its dissolution characteristics. A Plackett–Burman screening design was employed to screen various factors such as stabilizer type, stabilizer concentration, drug concentration, and solvent to antisolvent volume ratio, speed of mixing for their effect on mean particle size, saturation solubility and % drug released.

2. Materials

Glibenclamide (GLB) was obtained as a gift sample from Cadila Pharmaceuticals Limited (Ahmedabad, India). Polyvinyl Pyrrolidone S 630 D (copolymer of vinylpyrrolidine and vinyl acetate) (PD) was obtained as a gift sample from International Specialty Products, Singapore. Poloxamer 188 (coblock polymer of polyoxyethylene and polyoxypropylene) (PX) was obtained as a gift sample from Cadila Pharmaceuticals Limited (Ahmedabad, India). Tween 80, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), and hydroxyethylcellulose (HEC) were purchased from S.D. Fine Chemicals Limited (Mumbai, India). Analytical grades of acetone, dichloromethane, ethyl acetate, and isopropyl alcohol were purchased from S. D. Fine Chemicals Limited (Mumbai, India).

3. Methods

3.1. Preparation of GLB nanoparticles

GLB nanoparticles were prepared using a liquid antisolvent precipitation technique. GLB was dissolved in acetone at definite concentration and sonicated (bath sonicator, Trans-O-Sonic), for 20 s. The solution was filtrated through a 0.22 μ Whatman filter paper to remove possible particulate impurities. The prepared GLB solution was injected by syringe onto the tip of the antisolvent water containing each specific concentration of polymer and/or surfactant with stirring. Precipitation took place immediately upon mixing and formed a suspension with bluish appearance. The consequences of the formulation and process parameters, such as the type of solvent, the solvent/antisolvent ratio, the speed of mixing, and the concentration of GLB on the properties of the nanoparticles were investigated. The freshly formed suspension was centrifuged at 5000 rpm (Remi Centrifuge, Remi Instruments Pvt. Ltd) for 10 min and washed twice with 5 ml of deionized water; the obtained nanoparticles were then dried at 50 °C for 8 h and stored in desiccators till further use.

3.2. Experimental design

A set of experiments with Plackett–Burman (PB) screening design was adopted to develop the nanoparticles of GLB by liquid antisolvent precipitation method. PB designs are screening designs that involve a large number of factors and relatively few runs. They are the resolution three designs, so they can estimate only the main effects. They are typically used to identify a few significant factors out of a large set. A total of 12 experimental trials involving 5 independent variables were generated by Minitab® 16 (USA). The independent variables screened were the amount of PX (X1), amount of PD (X2), solvent to anti solvent volume ratio (S/AS) (X3), amount of GLB (X4) and speed of mixing (X5). Mean particle size (Y1), saturation solubility (Y2) and % DE 5_{min} dissolution efficiency after 5 min (Y3) were selected as the response variables on the basis of trials taken during preliminary batches.

3.3. Characterization of GLB nanoparticles

3.3.1. Mean particle size and zeta potential analysis

Mean particle size, size distribution and zeta potential of GLB nanoparticles were determined using Zetatrac (Microtrac Inc., USA). Zetatrac utilizes a high frequency AC electric field to oscillate the charged particles. The Brownian motion power spectrum is analyzed with modulated power spectrum (MPS) technique which is a component of power spectrum resulting from oscillating particles. 100 mg of sample was suspended with sufficient water and suspension samples

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