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Formulation and Pharmacokinetic Studies of Rapidly Dissolving Nanofibers

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Abstract: Diabetes is a group of metabolic diseases, characterized by high blood sugar. For complete absorption and good bioavailability of orally administered drugs, they should have good solubility. But, many drug molecules are not completely utilized because of their poor solubility and bioavailability. Dissolution of drugs is the rate-controlling step which determines the rate and degree of absorption. Drugs with slow dissolution rates generally show erratic and incomplete absorption leading to low bioavailability when administered orally. In present study, rapidly dissolving fibers of Glibenclamide (GLB) were formulated using PVP as fiber forming polymer. GLB, an anti-diabetic drug was selected for the study. Electrospinning method was used to formulate rapidly dissolving fibers. SEM result showed nanostructure of GLB (370nm-553nm). FTIR and DSC analysis revealed good drug polymer compatibility. *In vitro* drug release showed enhanced release profiles for rapidly dissolving nanofibers compared to pure drug and release patterns were found to be pH dependent.

Key words: GLB · Nanofibers · Electrospinning · Drug Release · DSC

INTRODUCTION

Nanosizing can be regarded as an established formulation approach to increase the bioavailability of poorly water-soluble compounds [1]. According to the food and drug administration nanoparticle drug is not a generic drug rather is considered as "new drug" molecule and is not bioequivalent to its microcrystalline or solubilised form administered at the same dose and therefore it can be patented [2]. GLB, a second generation sulfonylurea, is used in the treatment of non-insulin dependent diabetes mellitus (Type-II) [3]. GLB has established potential benefits such as lower dose, rapid onset, lower insulin levels and less-pronounced glucagonotropic effects, insulin-sensitizing and insulin-mimetic affects. The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step for absorption of drugs from the gastrointestinal tract [4]. GLB shows poor solubility in gastrointestinal fluids, which can give rise to variations in its dissolution rate and incomplete and/or unpredictable bioavailability. Its plasma half-life is 4-6 h, which makes multiple dosing to maintain the therapeutic blood level [5]. In order to improve dissolution and bioavailability of this drug, several strategies have been used, such as micronization, crystal habits of drug substances, use of surfactants and cyclodextrins, salt formation, molecular dispersion, use of prodrug etc [6].

Electrospinning is a popular procedure in scientific researches due to the ease of implementation, the cost-effectiveness of the process and the unique properties and potential applications of the resultant nanofibers [7]. The present work aims to evaluate the potential of the electrospinning for the development of fast dissolving nanofibers of GLB using Polyvinylpyrrolidone (PVP) as hydrophilic carrier and as the filament-forming matrix because it has been broadly reported to be used for enhancing solubility of a wide variety of poorly water-soluble drug and it has good electrospinnability in a series of typical organic solvents such as methanol, ethanol, chloroform and N, N-dimethylacetamide [8].

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MATERIALS AND METHODS

Materials:L GLB was received from, Samruddha Pharmaceuticals, Thane, Mumbai, India. PVP (Mw = 13, 00, 000) and Dialysis tubing cellulose membrane were obtained from Sigma-Aldrich, Germany. Methanol, Chloroform, NaH2PO4 and Na2HPO4 (Emplura), Merck Specialties Private Limited).

Preparation of GLB Nanofibers: The drug GLB (10w/v %) and the polymer PVP K30 (10 w/v %) were dissolved in solvent mixture of chloroform: methanol (1:3) separately. Above solutions were mixed together in 1:3 ratio. Mechanical stirring was done for 2h at 24°C to obtain homogeneous co dissolved spinning solutions. The solutions thus obtained were degassed for 10 min before using for the spinning processes. Spinning solutions were carefully loaded in a 2ml syringe; the positive electrode of the high voltage power supply was connected to the needle tip. The grounded electrode was connected to a metal collector wrapped with aluminum foil. The electrospinning process was carried out under ambient conditions (24±1°C and relative humidity 68 ±3%). A fixed electrical potential of 12 kV was applied across a fixed distance of 10 cm between the tip and the collector (2000rpm). The feed rate of solutions was controlled at 1.0 ml/h by means of a single syringe pump.

Physico-chemical Characterization of the Nanofibers: The surface morphology of the pure drug and drug embedded in the polymer fiber were characterized by Field emission scanning electron microscope (FESEM, FEI Sirion). They were mounted directly on to the SEM sample stub using double-sided sticking tape and coated with gold (thickness 200 nm) under reduced pressure (10-4 mm of Hg) at 5-30 KV. High resolution imagining was used for measuring fiber size. All the images were recorded at typical working distance of 8-10 mm. Fourier-transform infrared (FTIR) spectroscopy was conducted on Bruker Tensor 27, using KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 500-4000 cm^{-1} and the resolution was 2 cm^{-1}. The infra-red (IR) spectra of the sample GLB was compared with the IR spectra of the GLB reference provided in Indian Pharmacoepia. Differential Scanning Calorimetry (DSC) was performed with a Mettler-Toledo DSC 821e (Mettler-Toledo GmbH, Switzerland) instrument. DSC curves were evaluated with STAR e-Software supplied by the Mettler-Toledo company. The starting and final temperatures were 25 ^{0}C and 300 ^{0}C and heating rate was 10 ^{0}C /min. Argon atmosphere was used in all cases. Three parallel examinations were done from all samples. The instrument was calibrated using indium as reference material. Samples were measured in a 30 Rl aluminium pan.

***In vitro* Dissolution Studies:** *In vitro* dissolution studies were carried out in 600 ml pH 4, 6.4 and 7.8 phosphate buffer at 37 ±0.5 °C at 50 rpm (Paddle method, Electrolab Dissolution Tester TDT-06P, USP). 10 mg of GLB or its equivalent formulation was added to the dissolution medium and 4 ml of sample was withdrawn at 5, 10, 15, 30, 60, 120, 240 and 480 minutes and replaced with fresh media. The solutions were filtered (0.22 ìm) and concentration of the drug in release media was estimated using a double beam UV-visible spectrophotometer (Yu *et al*. 2012). Evolution 300 (Thermo Fisher Scientific, Madisson, WI, USA) operated by Vision Pro® software at 228nm by the regression equation of standard curve developed in the same media.

RESULTS AND DISCUSSION

Physico-Chemical Characterization of the Nanofibers: The surface morphology and diameter of nanofibers were studied by SEM (FEI Quanta 200). Results revealed that GLB nanofibers were in the range of 370-553 nm. Scanning electron micrographs of the pure drug GLB with low and high magnification images have depicted(Figure 1a and b). It is evident that the pure drug GLB has microstructure with grain size of 15 microns. Scanning electron micrographs of GLB loaded PVP with low and high magnification has been shown in (Figure 1c and 1d). It is apparent that the formed fibers at 10kV distance of 10 cm have diameter as low as 370 nm.

The FTIR spectrum of pure GLB (Figure 2a) presents NH stretch at the wave number of 3314 cm^{-1}, Aromatic-H absorption peak at the wave number of 3116cm-1 and C=O absorption peaks at 1715 cm-1.(Figure 2b) shows the standard FTIR spectrum of pure PVP. The FTIR spectrum of GLB nanofibers is represented in(Figure 2c) also presents all the absorption peaks produced by pure GLB and PVP. This indicates the absence of interaction between the drug and PVP.

From the DSC curves of the PVP, GLB and GLB nanofibers, it is evident that the polymer starts dissociating from 80°C onwards and finally at 156°C, which the melting point of PVP. On the other hand, we observed a broad endothermic peak for pure drug GLB at 156°C, where the drug has completely dissociated (Figure 3b). It is obvious that the combination of the PVP along with GLB has shown similar behavior as that of individual materials (Figure 3a/3b/3c).

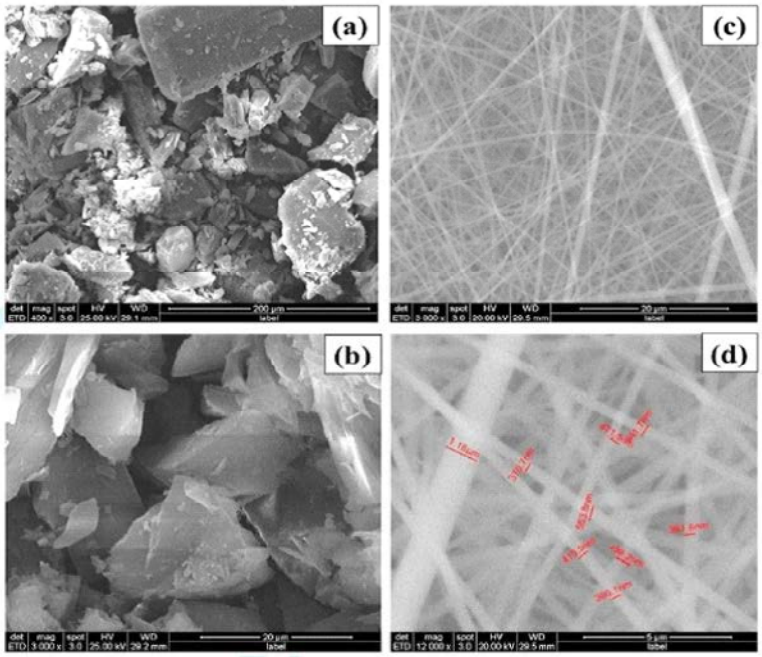

Fig. 1: SEM images of pure GLB drug (a) Low magnification (b) high magnification (c) low magnification of nanofibres and (d) high magnification of nanofibers.

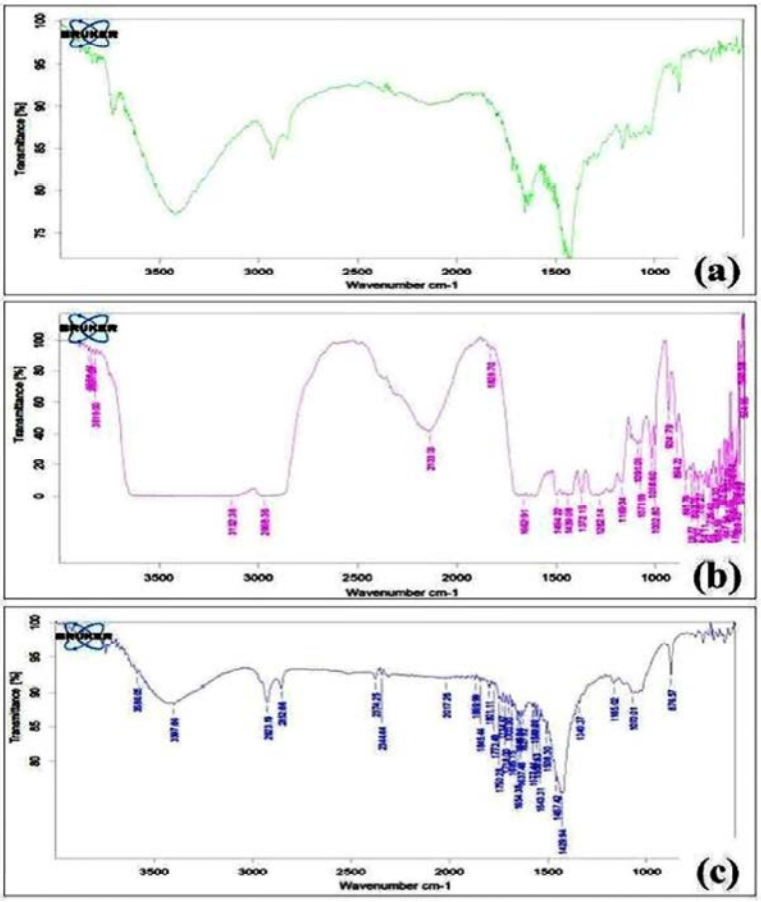

Fig. 2: FTIR spectra of (a)Pure polymer PVP, (b) Pure GLB drug and (c) GLB nanofibers.

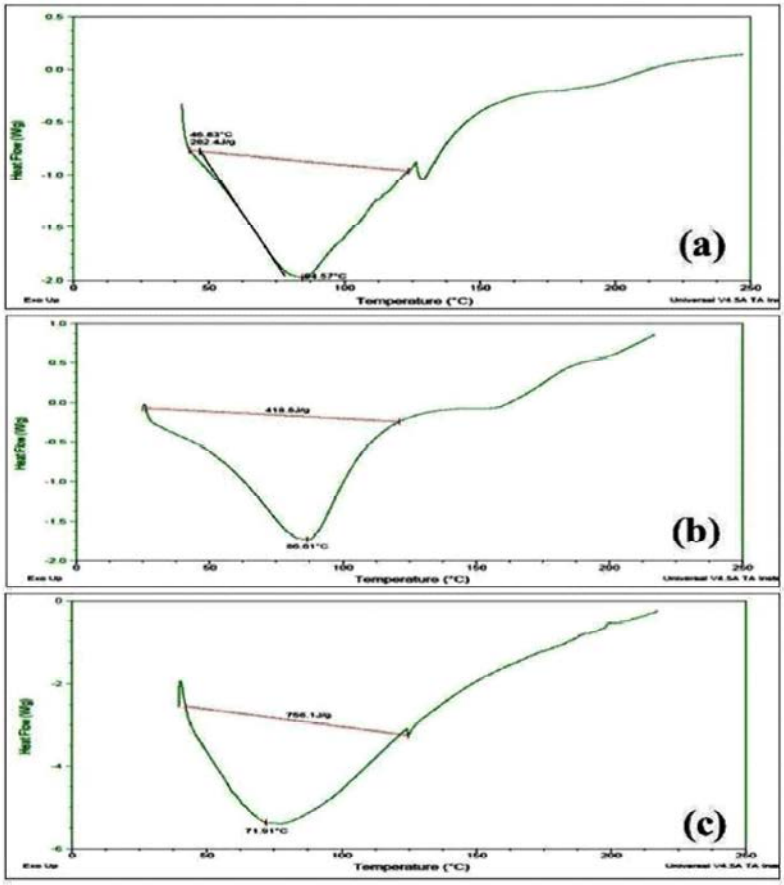

Fig. 3: DSC thermographs of (a) Pure polymer PVP, (b) Pure GLB drug (c) GLB nanofibers.

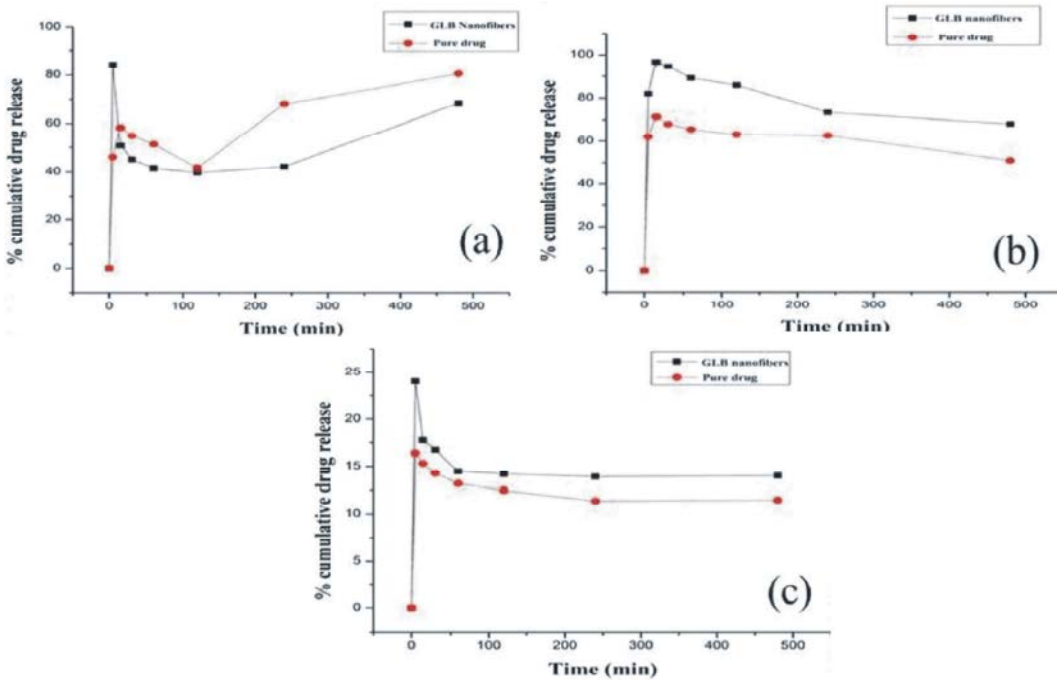

Fig. 4: Drug release profiles of nanofibers at pH (a) 7.8, (b) 6.4 and (c) 4

***In vitro* Drug Release:** The comparative (Nanodrug v/s pure drug) *In vitro* release profiles at pH 7.8, 6.4 and 4 are depicted in Figure 4 (a/b/c) respectively. The dissolution rates of the GLB were greatly influenced by the use of PVP. The release of GLB in the dissolution media was found to be a function of the percent of polymer load as well as the pH of the media. At respective pH (7.8, 6.4 and 4) maximum % release of drug from GLB nanofibers (82%, 95% and 24%) and from pure drug (58%, 72% and 17%) was noticed at 5 min. The better release profiles in the nanofibers may be partially described due to reasons such as high surface area of the polymer carrier matrix, enhanced porosity and the excellent wet ability of PVP. However, the release profiles varied with pH of the release medium.

CONCLUSION

In this study we prepared GLB loaded PVP nanofibers. The preparation PVP nanofibers are a simple technique that can be easily scaled up. SEM images confirm the canonize structure of drug loaded fibers and also it is evident that the drug is uniformly distributed in the fibers. FTIR result indicates the absence of interaction between the GLB and PVP. DSC result revealed similar thermostability status of GLB nanofibers, PVP and GLB. Invitro drug release profiles at pH 7.8, 6.4 and 4 shows that the drug release is enhanced with decrease in pH. In summary, GLB nanofibers could be a simple and useful approach for effective drug delivery to overcome the drawbacks of the conventional drugs. These nanofibers could be effectively used as oral fast dissolving formulation which show rapid onset of action with in upper part of Gastro Intestinal tract with increased solubility and bioavailability.

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