



Enhancement of solubility and dissolution rate of glibenclamide using poloxamer – 407 as carrier

Ramanpreet Kaur*, Sandeep Kumar

ASBASJSM College of Pharmacy, Bela, Ropar, India

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ABSTRACT

The purpose of present study is to increase the solubility and dissolution rate of Glibenclamide, a poorly water soluble drug by lyophilization technique using a hydrophilic carrier, poloxamer-407. The prepared lyophilization product showed an enhancement in solubility and dissolution rate. Lyophilized products were characterized with Infrared spectroscopy, X-ray diffraction and scanning electron microscopy. These techniques revealed that increase in solubility and dissolution rate of glibenclamide is due to decrease in crystallinity of the drug. In conclusion formulation of glibenclamide lyophilized product with water soluble polymer could be a suitable approach to improve solubility and dissolution rate of glibenclamide.

Keywords: Glibenclamide, Solid dispersion, Poloxamer, Crystallinity, Dissolution, Diffraction.



INTRODUCTION

Biopharmaceutical Classification System Class II has low solubility that is rate-limiting step in case of drug absorption, drug bioavailability and pharmacological effects. Glibenclamide is an example of such compounds^[1], antidiabetic agent belongs to second- generation sulfonyl urea group and used in type II diabetes that is non-insulin dependent. It stimulates the insulin release from beta cells of pancreas. Various technologies have been used to improve the dissolution rates of water insoluble drugs and results in increase the bioavailability of drug by reducing dosage frequency when administered through oral route. But the lyophilization method is effectively used because of its advantage that it is suitable for thermo-sensitive drugs.^[2-5] Lyophilized product of poorly water insoluble drugs with lipophobic carrier matrix have been reported to improve their solubility and dissolution rate.^[6-8] Different types of water-soluble carriers have been used for preparation of solid dispersion of poorly water soluble drugs.^[9-11] Polyethylene glycol, polyvinyl pyrrolidone, Lactose, β - cyclodextrin and hydroxypropyl methylcellulose^[12-15] are common water-soluble polymers. Now, Poloxamers, a group of block co-polymer non-ionic surfactants have been used in the preparation of solid dispersions^[16,17] which are used as emulsifiers, solubilising agents and suspension stabilizers in

liquid, oral, topical and parenteral dosage forms and also act as wetting agents and plasticizers and have been reported for enhancing the solubility and bioavailability of poorly water soluble drugs in solid dosage forms.

Lyophilization is considered better technique to attain the amorphous form of different pharmaceutical compounds.^[16-18] This technology is advantages by retention of form and activity, ease of reconstitution, good stability of product as well as precise dosing of pharmaceutical ingredients.

In the present study, PXM-407 was selected as a hydrophilic carrier for its excellent surfactant properties and oral safety. The lyophilization (freeze drying) method was used to prepare GLM – PXM-407 SDs in a relatively, easy simple, rapid and reproducible manner and the formulated SDs were evaluated for their solubility and *in-vitro* dissolution rates.^[19-25]

MATERIAL AND METHODS

Glibenclamide (GLM) was received as a gift sample from BR Medi. Lab. Baddi and Poloxamer-407 [PXM-407], Cross Carmellose Sodium (CCS) and microcrystalline cellulose (MCC) were procured from Signet Chem. Pvt Ltd., Mumbai and Methanol was procured from S.D. Fine chemicals

*Corresponding Author Address: Ramanpreet Kaur, Registered Pharmacist, Punjab, India; E-mail: ramanpreet664@gmail.com

Mumbai. All reagents used were of analytical grades.

Preparation of lyophilized formulations: GLM and PXM – 407 were taken in different ratio's (1:1, 1: 3 and 1:5 w/w) for preparation of solid dispersions by lyophilization method. GLM was weighed and dispersed into 100ml PXM solution and the dispersion being stirred with the help of a magnetic stirrer. Then 25% liquid ammonia was added drop-wise and stirred until a clear solution was obtained. The sample was lyophilized in a lyophilization chambers at a temperature of -40°C and vacuum of 9×10^{-3} M bar. The lyophilized product then sifted through 60 mesh sieve and stored in an air tight containers until further evaluations.

Characterization of lyophilized solid dispersions:

Solubility studies: An excess amount of Pure Glibenclamide and solid dispersions equivalent to 10 mg of glibenclamide was added to 10 ml of phosphate buffer (pH-6.8) in a volumetric flasks. The volumetric flasks were capped properly and shaken at $37 \pm 2^{\circ}\text{C}$ in a temperature controlled water bath (shaking water bath) for 48 h. Resultant samples containing undissolved solid dispersions suspended in the volumetric flasks were filtered through Whatman filter paper no.41 and then diluted with phosphate buffer pH6.8 and analyzed by UV- visible spectrophotometer at 302.5 nm.

In-vitro dissolution studies: *In-vitro* dissolution studies of glibenclamide and its solid dispersion alone were carried out using USP II apparatus. Powdered samples equivalent to 10 mg of glibenclamide were added to 900 ml of dissolution medium (Phosphate buffer pH – 6.8) maintained at $37 \pm 0.5^{\circ}\text{C}$ and stirred at 50 rpm. 5ml aliquot of sample was withdrawn at 5, 10, 15, 20, 25, 30 mins and replaced by 5ml of fresh dissolution media. The collected samples were analyzed after filtration at 302.5 nm using UV- visible spectrophotometer against the blank sample.

Fourier transforms infrared (FTIR) spectroscopy: Fourier transform infrared (FTIR) spectra of pure drug, Poloxamer-407 solid dispersion prepared by lyophilized method were recorded on Bruker (alpha E). The scanning range was $4000-400\text{ cm}^{-1}$.

Powder X-ray diffraction (XRD) analysis: Powder X-ray diffraction (XRD) pattern of pure drug and solid dispersion prepared by lyophilization method were recorded using PW 1729 X-ray diffractometer. Under the following

conditions target $\text{CuK}\alpha$ monochromatized radiation, voltage 45KV, and current 40 mA at ambient temperature. The results were collected in the continuous scan mode using a step size of 0.017° at 2θ /s. Scanned range was $5-50^{\circ}$.

Scanning electron microscopy (SEM): The external morphology of pure drug, Poloxamer-407 and solid dispersion prepared by lyophilization method were examined under a scanning electron microscope JSM 6100 JEOL JAPAN.

RESULT AND DISCUSSION

Solubility Profile : Comparison of solubility data of pure drug and solid dispersions (1:1,1:3 and 1:5 w/w) prepared by lyophilization method in phosphate buffer (pH 6.8) at $37 \pm 2^{\circ}\text{C}$.

Table 1 : Solubility data of pure drug and solid dispersion prepared by lyophilization method.

Formulation code	Solubility($\mu\text{g/ml}$)
Pure drug	72.85 ± 0.001
SDL1	209.04 ± 0.002
SDL3	260.00 ± 0.006
SDL5	215.71 ± 0.012

In-vitro dissolution studies: The dissolution profile of pure drug and solid dispersion prepared by lyophilization method were carried out in phosphate buffer (pH 6.8) shown in Fig. 1.

Fourier transforms infrared (FTIR) spectroscopy: The FTIR studies were performed to check the possible interaction of the drug with the carrier. The spectrum of pure Glibenclamide depict the characteristic peaks at 3315.28 cm^{-1} corresponding to N-H stretching, at 1708.69 cm^{-1} corresponding to C=O (ketone) stretching, at 1611.33 cm^{-1} corresponding to C=C (alkene) stretching, at 1337.95 cm^{-1} corresponding to C-N(amines) stretching, at 1275.47 cm^{-1} corresponding to C-OH stretching, at 1059.58 cm^{-1} corresponding to S=O stretching. While FT-IR of Poloxamer-407 shows peaks at 2879.42 cm^{-1} corresponding to C-H stretch, at 1100.56 cm^{-1} corresponding to C-O(ether) stretch, at 3251.58 cm^{-1} corresponding to O-H stretching vibrations. The FT-IR spectra of dispersions showed almost all the characteristic peaks of the drug and Poloxamer-407, without affecting their peak position which indicated lack of interaction between the drug and the polymer shown in Fig. 2 – 4.

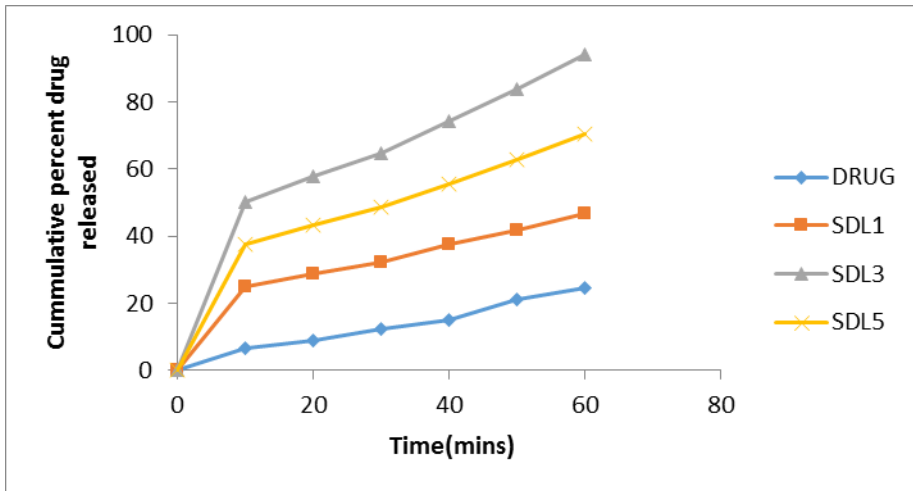


Fig. 1 : Percentage released of pure drug and from lyophilized product ratio's (1:1, 1:3, 1:5)

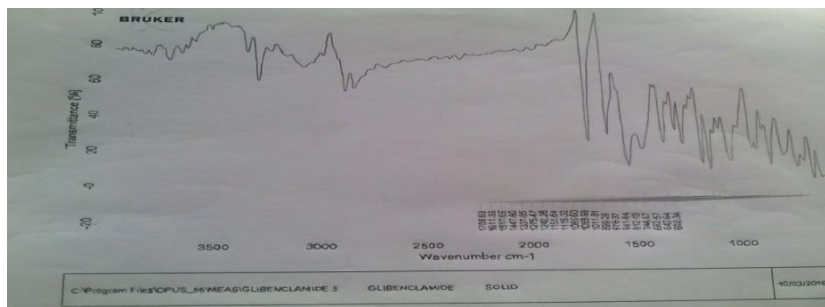


Figure 2 : FTIR spectra of Glibenclamide

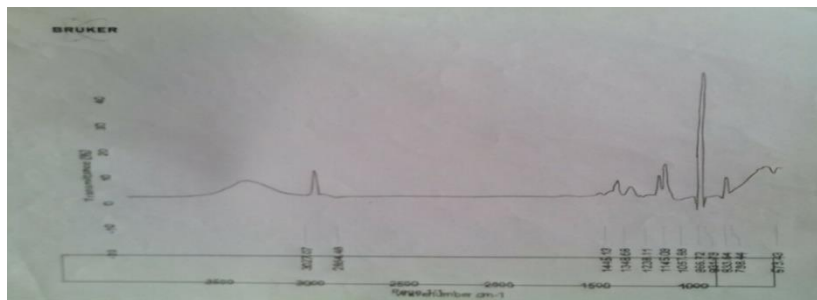


Fig 3: FTIR Spectra of Poloxamer-407

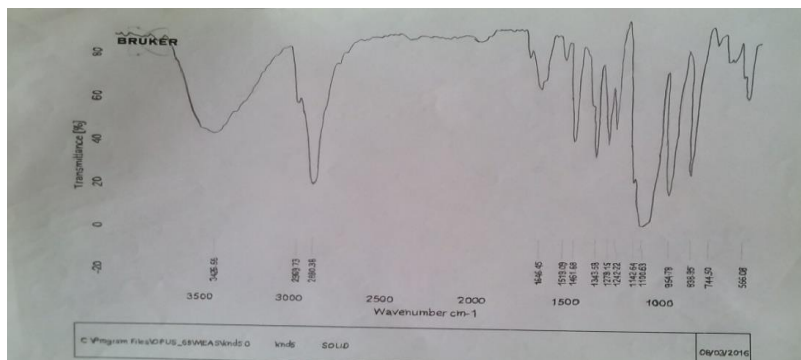


Fig. 4 : FTIR spectra of solid dispersion(1:3) prepared by lyophilized method

Powder X-ray diffraction (XRD) analysis:

Powder XRD patterns of pure drug and best solid dispersion (SDL3) prepared by Lyophilization method are shown in fig. 5 and 6. The XRD pattern of pure drug presents several diffraction peaks indicating the crystalline nature. Diffraction peaks of pure drug were observed at 2θ values of 10.954, 11.769, 12.633, 14.856, 15.309, 16.704. The polymer showed absence of the peak and XRD of SDL3 showed missing of peaks, it indicated that the drug changed from crystalline to amorphous nature. Decrease in crystallinity of the drug and polymer in dispersion may contribute to the enhancement of dissolution of the drug.

Scanning electron microscopy (SEM): SEM images of Glibenclamide, Poloxamer-407 and best solid dispersion prepared by lyophilization method (SDL3) in fig.7 - 8. Glibenclamide crystals are regular eblongated in shape and poloxamer-407 crystals are spherical in shape. In case of SEM of solid dispersions (SDL3) indicates the difficulty to distinguish the Glibenclamide crystal. The polymer had formed a uniform coating over the individual drug particles thus resulting in the formulation of irregular shape particles, it indicated that the drug changed from crystalline to amorphous nature.

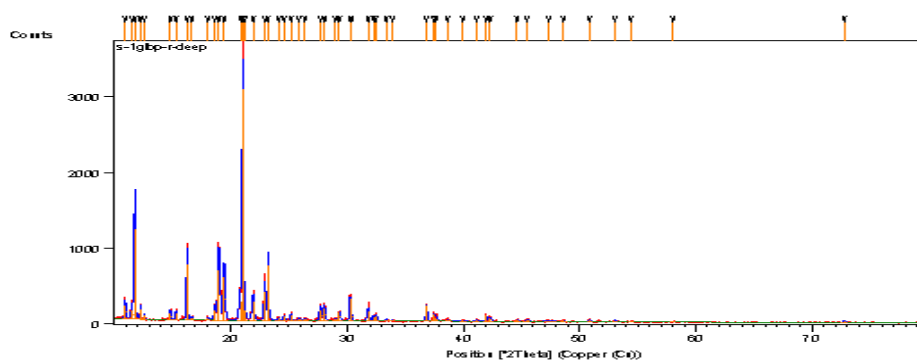


Fig. 5: XRD Spectra of Glibenclamide

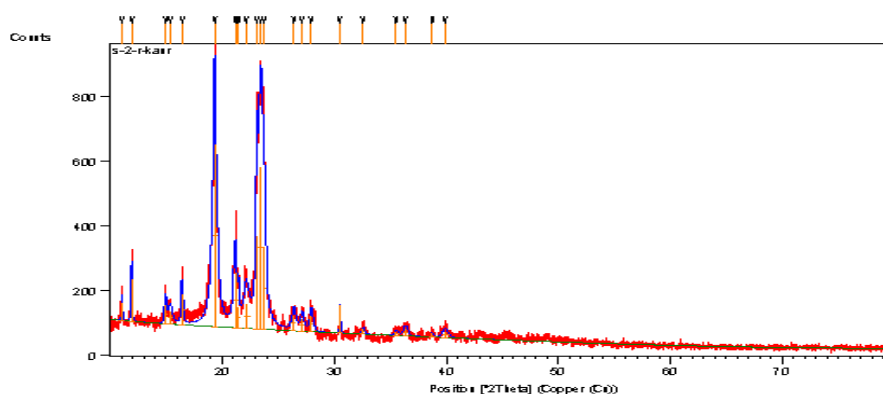


Fig. 6 : XRD Spectra of Lyophilized product(1:3) Scanning

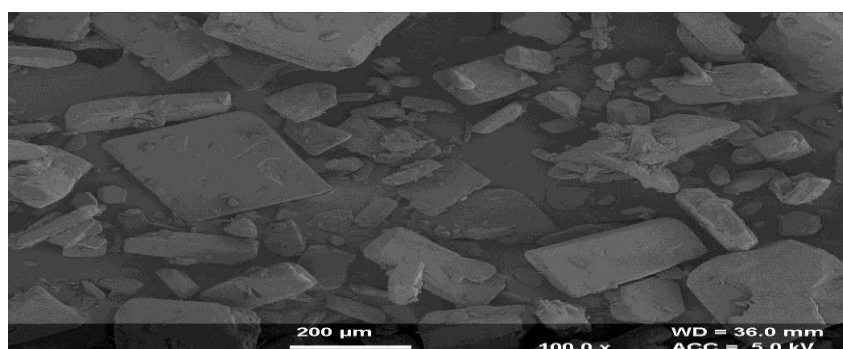


Fig. 7: SEM of pure drug Glibenclamide

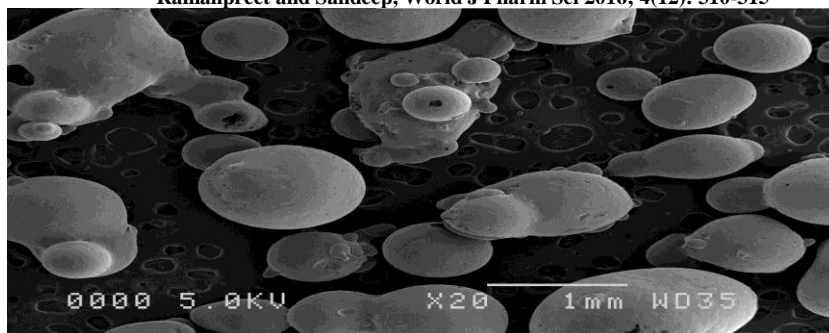


Fig. 8 : SEM of Poloxamer-407

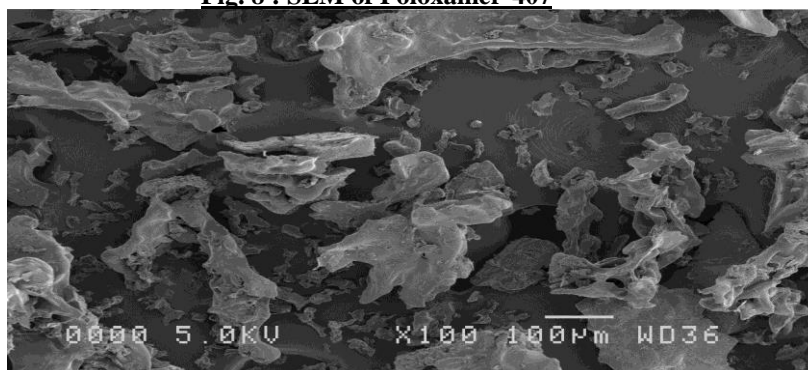


Fig. 9 : SEM of SDL3

CONCLUSION

It can be concluded that lyophilization is a perfect technique for improving the solubility and dissolution rate of glibenclamide. The dissolution rate of pure drug was 22.41% in 60 min. and best lyophilization product ratio (1:3) SDL3 showed 93.98% in 60 min. The FT-IR spectra of lyophilized product SDL3 showed almost all the characteristic peaks of the drug and Poloxamer-407, without affecting their peak position which

indicated lack of interaction between the drug and the polymer. XRD of SDL3 shows missing of peaks. In case of SEM of (SDL3) indicates the difficulty to distinguish the glibenclamide crystal. It indicated that the drug changed from crystalline to amorphous nature. From the results of characterization of lyophilized product it is clear that glibenclamide crystalline drug particles converted into an amorphous form results in increases solubility and dissolution rate of glibenclamide.

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