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RESEARCH ARTICLE

IN VITRO DISSOLUTION STUDY OF GLIMEPIRIDE FROM BINARY AND TERNARY SOLID DISPERSION FORMULATION

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Abstract

Objective: Glimepiride (GMP) is poorly water soluble drug, so solubility is the main constraint for its oral bioavailability. Because, poor aqueous solubility and slow dissolution rate of the glimepiride lead to irreproducible clinical response or therapeutic failure in some cases due to sub therapeutic plasma drug levels.
Methods: In this study, binary and ternary solid dispersion of glimepiride were prepared with polyethylene glycol 6000 (PEG 6000) and polyethylene glycol 4000 (PEG 4000) at different weight ratios using the solvent evaporation and melting method.
Results: It was found the drug was released 0.46% after 5 minutes and only 15.83% within 60 minutes from active glimepiride on the other hand the release pattern of glimepiride from the binary formulation containing PEG 4000 in 1:5 (Formulation coding: G5) showed the best result.
Conclusion: It was found that the ternary different SD formulation containing (PEG4000: Glimepiride: Povidone) in ratio 1:1:0.25 (Formulation G13) showed the best result. The drug was changed to amorphous form after solid dispersion. It was also evident that solid dispersions improve solubility of drug particles thus enhancing dissolution characteristics of drugs they increase the oral bioavailability.
Keywords: Fusion method, glimepiride, poorly soluble drug.

INTRODUCTION

It has studied that, improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Most of the newly invented chemical entities are poorly water soluble. As a result formulating them as oral solid dosage forms is a hurdle to the specialists. Many techniques have been exercised to improve oral bioavailability of drugs1. The rate of dissolution and solubility should not be confused as they are different concepts, kinetic and thermo-dynamic, respectively. The solubilization kinetics, as well as apparent solubility can be improved after complexation of an active ingredient with cyclodextrin. This can be used in the case of drug with poor solubility2. The oral route of administration is the most preferred and widely acceptable route of delivery due to ease of ingestion for many drugs. Drugs with slow dissolution rate show the incomplete absorption leading to low bioavailability when orally administered3. Many of the drugs belong to class II of the biopharmaceutical classification system showing poor solubility and high permeability Glimepiride shows low, pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37°C (<0.004 mg/ml). In media pH>7, solubility of drug is slightly increased to 0.02 mg/ml. These poor water soluble drugs provide challenges to deliver them in an active and absorbable form to the desired absorption site using physiologically safe excipients Therefore; one of the most important steps in the development of dosage forms for these drugs is to improve their solubility and/or dissolution rate. Chiou and Rigelman and Serajuadin *et al.*, have used the solid dispersion (SD) technique for dissolution enhancement of poorly water-soluble drugs4. Among the various approaches, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active

pharmaceutical ingredients because it is simple, economic, and advantageous. Sekiguchi and Obi were the first to propose the SD method using water-soluble carriers to improve the dissolution characteristics of poorly water-soluble drugs. Many water-soluble carriers have been employed for preparation of SD of poorly soluble drugs5. The most common are polyethylene glycols, polyvinyl pyrrolidone, mannitol and hydroxypropyl methylcellulose. Due to poor solubility in GI fluids, it results in low and erratic oral bioavailability6. Glimepiride was selected as a model drug for dissolution enhancement studies in the present investigation. Attempts were made to enhance the dissolution of GMP using a SD technique. SDs of GMP with PVP K 30 was prepared in different ratios using solvent evaporation method and then tablets of best formulation of SD were formulated by using direct compression method7. Tablet formulations were prepared by direct compression technique using super disintegrates povidone in different concentrations8. Glimepiride is a poorly water-soluble oral hypo-glycemic drug exhibiting poor dissolution pattern9. The purpose of this work was to increase the dissolution rate of glimepiride by formation of solid dispersion with different water soluble carriers. Solid dispersion of glimepiride were prepared with polyvinyl pyrrolidone K-30, poloxamer 407, polyethylene glycol 6000 (PEG 6000), polyethylene glycol 4000 (PEG 4000), sodium starch glycolate, ludiflash and lactose at different weight ratios using the solvent evaporation and melting method[10]. Physical mixtures of the poloxamer 407 and povidone K-30 with glimepiride at different ratios were also used. In compare to physical mixtures with povidone K-30 and poloxamer 407, drug release from physical mixture PM (1/9) PVP K-30 was higher (65.93% within 5 min) than drug release from physical mixture with poloxamer 407 (56% within 5 min) the drug release from pure drug was 6.84% within 5 min[11]. With the recent development in the screening of potential therapeutic agents, the number of poorly water soluble drugs have risen sharply and gained large interest due to the challenges in the oral solubility of the drug which leads to the major cause for which the techniques are meant to be implemented. One amongst such techniques is the formulation of solid dispersion for the solubility enhancement[12,16,18].

MATERIALS AND METHODS

Glimepiride was obtained from Eskayef Bangladesh ltd, Gazipur. PEG 4000, PEG 6000 were obtained from Albion laboratories ltd, Eudragit was obtained from The Acme laboratories ltd. Other reagents used were of analytical grade.

Preparation of solid dispersion formulation

Fusion method was used for the preparation of solid dispersion of glimepiride. Desired amount out of drug and polymers in different ratio were weighted out accurately and taken in a beaker and melted at 70°C.

The mixture was stirred vigorously for uniform mixing and was kept in normal room temperature for 72 hour until a solid mass was formed. Solidified mixture was then grinded thoroughly with the help of mortar and pestle. Then the powdered particle passed through a sieve (mesh size 40).

Figure 1: Solid dispersion formulations of different batches.

The resulted solid dispersion formulations were weighted and transferred in a fresh vial and kept in a dessicator until further investigation.

Table 1: Formulation of binary and ternary solid dispersion of glimepiride prepared by fusion method using different polymer at different ratio.

Batch	Carriers	Drug polymer ratio	Dispensing (mg)
G1	PEG4000	1:1	300:300
G2	PEG4000	1:2	300:600
G3	PEG4000	1:3	300:900
G4	PEG4000	1:4	300:1200
G5	PEG4000	1:5	300:1500
G6	PEG6000	1:1	300:300
G7	PEG6000	1:2	300:600
G8	PEG6000	1:3	300:900
G9	PEG600	1:4	300:1200
G10	PEG6000	1:5	300:1500
G11	PEG4000:GLM: POVIDONE	1:1:0.75	200:200:150
G12	PEG4000:GLM: POVIDONE	1:1:0.50	200:200:100
G13	PEG4000:GLM: POVIDONE	1:1:0.25	200:200:50
G14	PEG4000:GLM: POVIDONE	1:1:00	200:200:00
G15	PEG6000:GLM: POVIDONE	1:1:0.75	200:200:150
G16	PEG60000:GLM: POVIDONE	1:1:0.50	200:200:100
G17	PEG600:GLM: POVIDONE	1:1:0.25	200:200:50
G18	PEG600:GLM: POVIDONE	1:1:00	200:200:00

***In-vitro* dissolution test for Glimepiride and solid dispersion formulation**

The *in vitro* dissolution studies for Glimepiride drug and SD formulation were performed using USP dissolution test apparatus type II (paddle type) method using 900 ml of phosphate buffer (pH 7.8) as dissolution medium. The temperature of the medium was maintained at (37±0.5°C) throughout the experiment. The samples contained glimepiride or its

equivalent solid dispersion were placed in the dissolution medium. Paddle was used at a stirring rate of 75 rpm. A 5 ml aliquot was withdrawn at predetermined time intervals of 5, 15, 30, 45, and 60 min and then 5 ml of fresh dissolution medium was replaced to maintain the constant volume of dissolution medium. The absorbance value of the collected samples was measured at 273 nm using UV-visible spectrophotometer against dissolution medium as blank. The percent release of drug was calculated using the equation obtained from the standard curve in the media[19].

RESULTS AND DISCUSSION

The aims of present investigation was to enhance the dissolution rate of poorly water soluble drugs glimepiride by preparing the solid dispersion using povidone, PEG 4000, PEG 6000. In current study18 SD dispersion formulations of glimepiride were prepared by Fusion method using different soluble polymers. When glimepiride were dispersed in polymer, its dissolution were enhanced significantly compared with active glimepiride.

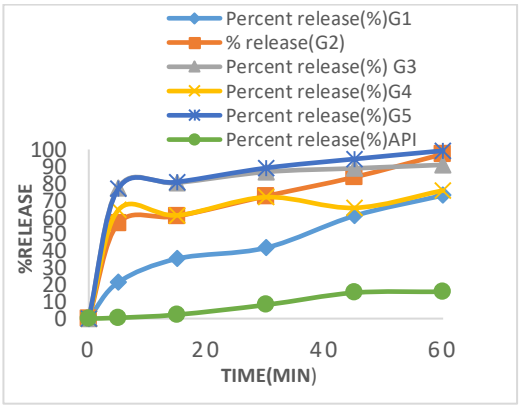

Figure 2: Average % release of drug from binary SD formulation containing PEG 4000 with different ratio.

In this study fusion/melting method was used for the preparation of solid dispersion of glimepiride**.**

Dissolution profile of active Glimepiride

10 mg of pure Glimepiride was used for dissolution study.

It was found that only 0.46% drug was released after 5 minutes and 15.83% was released within 60 minutes time interval. This showed that dissolution profile of glimepiride was very poorly.

***In vitro* dissolution study of binary and ternary solid dispersion of glimepiride (fusion method)**

Solid dispersion of glimepiride with PEG 4000 at different ratio G1 (1:1), G2 (1:2), G3 (1:3), G4 (1:4), G5 (1:5) and active glimepiride (API) were used for dissolution study. It was found that only 0.46% from active glimepiride, 21.46% from formulation G1, 56.30% from G2, 77.30% from G3, 64.15% from G4 and 76.84% from G5, were released after 5 min and 60.77% from G1, 83.66% from G2, 88.83% from G3, 65.47% from G4, 94.36% from G5, 15.29% from active glimepiride were released after 45 min. Finally 72.88% from G1, 97.27% from G2, 90.91% from G3, 75.75% from G4, 99.76% from G5 were released within an hour time interval.

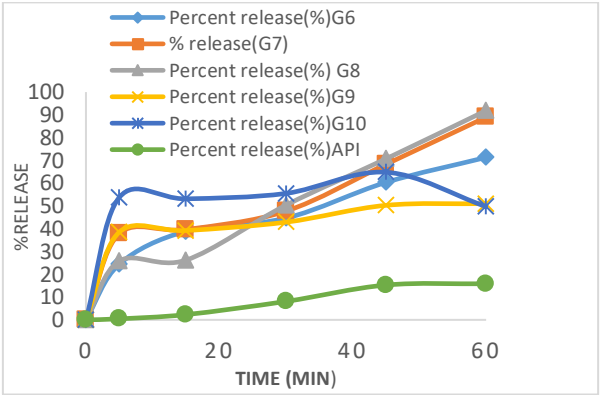

Figure 3: Average % release of drug from SD formulation containing PEG 6000 with different ratio

Whereas only 15.83% was released from active glimepiride in 1 hour. From the obtained data (Figure 2) we can conclude that, the release pattern of drug from SD formulation containing PEG 4000 has increased gradually when the amount of PEG 4000 was increased. It was observed that solid dispersion formulation G5 showed substantially better result in 1:5 ratio in comparison to those of G1, G2, G3, and G4.

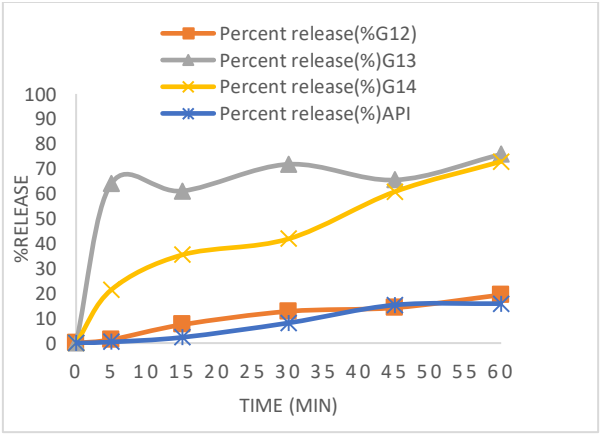

Figure 4: Average % release of drug from ternary SD formulation containing PEG 4000 and Povidone.

Comparative dissolution profile of active glimepiride and solid dispersion formulation (Glimepiride+PEG 6000) for their different ratio.

Solid dispersion of glimepiride with PEG 6000 at different ratio G6 (1:1), G7 (1:2), G8 (1:3), G9 (1:4), and G10 (1:5) were used for dissolution study. It was found that 24.46% from G6, 37.86% from G7, 25.84% from G8, 38.53% from G9, 53.76% from G10 were released after 5 min and 60.36% from G6, 68.30% from G7, 70.72% from G8, 50.28% from G9, and 64.82% from G10 were released after 45 min. Finally 71.31% from G6, 88.99% from G7, 91.87% from G8, 51.01% from G9 and 49.71% from G10 were released within an hour time interval. From the obtained data (Figure3) it was found that, the release pattern from SD

formulation containing PEG 6000 has increased gradually when the amount of PEG 6000 was decreased. It was observed that solid dispersion formulation G8 showed their better result in 1:3 ratios in comparison to those of G6, G7, G9, and G10.

Comparative dissolution profile of active glimepiride and solid dispersion (Glimepiride+ PEG 4000+ Povidone) for their different ratio

Ternary SD formulation of Glimepiride containing PEG 4000 and Povidone at different ratios of G11 (1:1:0.75), G12 (1:1:0.50), G13 (1:1:0.25), G14 (1:1:0) and API were used for dissolution study. It was found that 6% from G11, 1.38% from G12, 64.15% from G13, 21.46% from G14 and 0.46% from API were released after 5 min and 11.48% from G11, 14.19% from G12, 65.47% from G13, 60.77% from G14, 15.29% from API were released after 45 min. Finally 24.69% from G11, 19.35% from G12, 75.75% from G13, 72.88% from G14 and 15.83% from API were released in an hour time interval.

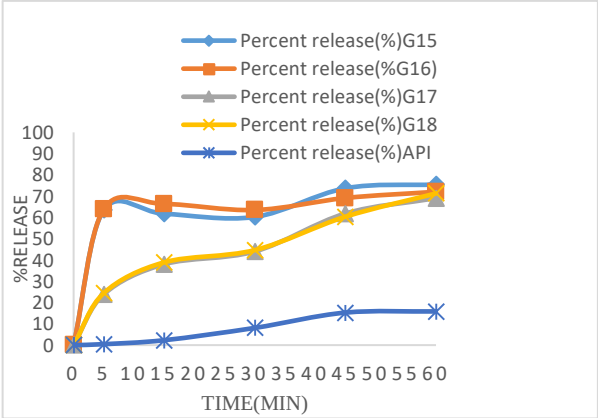

Figure 5: Percent release from ternary SD formulations of glimepiride containing PEG 6000 and Povidone.

From the obtained data (Figure 4) we can conclude that the release pattern from the glimepiride containing two water soluble polymer PEG 4000 and Povidone have increased gradually when the amount of second polymer povidone were decreased in different ratio. It was observed SD formulation G13 (1:1:0.75) gave the best result in comparison to those of G11, G12, G14.

Comparative dissolution profile of pure glimepiride and solid dispersion formulation (Glimepiride+ PEG 6000+ Povidone) for their different ratio

Ternary SD formulation of Glimepiride containing PEG 6000 and Povidone at different ratio of G15 (1:1:0.75), G16 (1:1:0.50), G17 (1:1:0.25), G17 (1:1:0) and API were used in dissolution study. It was found that 63.46% from G15, 63.92% from G16, 23.90% from G17, 24.46% from G18 and 0.46% from API were released after 5 min and 73.71% from G15, 69.14% from G16, 61.84% from G17, 60.36% from G18, 15.29% from API were released after 45 min. Finally 75.50% from G15, 72.06% from G16, 69.09% from G17, 71.31% from G18 and 15.83% from API were released in an hour interval.

From the obtained data (Figure 5) we can conclude that the release pattern from the glimepiride containg two water soluble polymer PEG 6000 and Povidone has increased gradually when the amount of second polymer povidone were increased in different ratio. It was observed SD formulation G15 (1:1:0.75) gave the best result in comparison to those of G16, G17, G18.

Effect of the polymer on the improvement of solubility and dissolution rate of poorly water soluble glimepiride

From the above analysis of the result showed in figure number all of the formulation of soliddispersion of glimepiride successfully made their enhancement of release profile of active glimepiride. It was proved that the water soluble polymers were exclusively able to change the drug in the micro level and finally crystal glimepiride was formed to the amorphous state. There is lots of effect to increase the solubility of poorly water soluble drug. Such as polyethylene glycol (PEG) have the ability to solubilize the drug and improve wettability. The solid dispersion of glimepiride with PEG 6000 and PEG 4000 may be useful to increase the stability, solubility, dissolution and bioavailability of poorly water soluble drug. Another povidone is suitable for the manufacturing of solid dispersion as it possesses forms water soluble complexes with many active drugs. It also act as binder, bioavailability enhancer and taste master[13,14].

Eudragit has a lower content of quaternary ammonium group in the structure and is considered as more permeable to water. Poloxamer act as solubilizing agent and plasticizer for enhancing the solubility and bioavailability of poorly soluble drugs in solid dosage forms. These water soluble polymers may operate in the micro environment immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in short time thus enhancing the solubility and dissolution of drug. Finally it can be concluded that dissolution rate of glimepiride was increased by solid dispersion technique which is due to the wettability and spread ability of the precipitated drug by reducing aggregation in the readily soluble state[17].

CONCLUSIONS

Solid dispersion has attracted considerable interest as an efficient means of improving the dissolution rate and bioavailability of hydrophobic drugs. Glimepiride is an oral blood sugar-lowering drug in a class of medicine for controlling diabetes called Sulfonylurea. In the present study, solid dispersions of Glimepiride with different hydrophilic carriers in different ratios were prepared by physical mixing and fusion method to improve water solubility and dissolution characteristics. The preparation of solid dispersion of Glimepiride by fusion method has been proven to be successful. This research showed that when Glimepiride was dispersed in suitable water-soluble carriers such as PEG 6000, PEG 4000 and Povidone. Its dissolution was enhanced as compared with pure drug. It was found the drug was released 0.46% after 5 minutes and only 15.83% within 60 minutes from

active glimepiride on the other hand the release pattern of glimepiride from the binary formulation containing PEG 4000 in 1:5 (Formulation coding: G5) showed the best result. It was found that the ternary different SD formulation containing (PEG4000: Glimepiride: Povidone) in ratio 1:1:0.25 (Formulation coding were: G13) showed the best result. *In-vitro* dissolution data also proves that percent release of drug from binary SDs was not similar with ternary SDs. The water soluble carrier may operate in the micro environment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in short time thus enhancing the solubility and dissolution of drug.

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AUTHOR'S CONTRIBUTION

Akhter S: writing original draft, methodology, investigation. **Hossen MS:** formal analysis, data curation, conceptualization. **Salahuddin M:** writing, review and editing. **Sunny MA:** supervision, methodology, formal analysis. **Sathi FA:** data curation, conceptualization. **Islam MS:** writing, review, and editing. All the authors approved the finished version of the manuscript.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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