EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 8
986-994
Year: 2017

IMPROVEMENT IN SOLUBILITY AND DISSOLUTION RATE OF GLIMEPIRIDE USING MELTABLE HYDROPHILIC CARRIERS

Amaresh Chandra Sahoo[1*], Sunil Kumar Kanungo[2], Subas Chandra Dinda[3], Jnyanaranjan Panda[4] and Ch. Niranjan Patra[4]

[1]School of Pharmaceutical Education and Research, Behampur University, Berhampur, Ganjam, Odisha, India.
[2]Institute of Pharmacy and Technology, Salipur, Cuttack, Odisha, India.
[3]College of Health Sciences, Mekelle University, Mekelle, Ethiopia.
[4]Roland Institute of Pharmaceutical Sciences, Khodasingi, Berhampur, Ganjam, Odisha, India.

***Corresponding Author: Amaresh Chandra Sahoo**
School of Pharmaceutical Education and Research, Behampur University, Berhampur, Ganjam, Odisha, India.

Article Received on 21/06/2017 **Article Revised on 11/07/2017** **Article Accepted on 01/08/2017**

ABSTRACT
Glimepiride is a third generation of hypoglycemic drug useful in the treatment of non-insulin dependent diabetes mellitus It is a white crystalline powder, relatively insoluble in water, exhibits slow GI absorption rate and poor bioavailability. The objective of the present research is to improve the solubility and dissolution rate of glimepiride using meltable hydrophilic carriers like PEG 6000, PEG 10000 and gelucire 44/14. Phase solubility studies showed negative ΔG_{tr}^{0} values for all the 3 carriers at various concentrations (0-5% w/v), indicating the spontaneous nature of solubilization. The solid dispersion exhibiting highest solubility (F8) was formulated into a rapidly dissolving minitablet using sodium starch glycolate as superdisintegrant. FT-IR and DSC studies revealed that glimepiride is compatible with carriers used in this study. The minimum quantity of neusilin US2 required for achieving the desired flowability and compressibility was 0.5 parts of carrier. Q_{30} values for formulation F13 showed more than 10 fold increase in dissolution rate compared to glimepiride. The rapidly dissolving minitablets of glimepiride were prepared successfully with a dissolution rate of more than 85% in 30 min.

KEY WORDS: PEG6000, PEG10000 and gelucire 44/14.

INTRODUCTION
Glimepiride is a third generation of hypoglycemic sulfonylurea which is useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM).[1] Prior reports reveal that the drug shows more potential benefits over currently available sulfonylureas such as lower dose, rapid onset of action, longer duration of action and lower insulin C-peptide level.[2] Glimepiride is a white crystalline powder, relatively insoluble in water (pKa=6.2). Glimepiride exhibits slow GI absorption rate and inter individual variations in its bioavailability due to its poor water solubility.[3] Several approaches have been reported for enhancement of solubility and dissolution of poorly soluble drugs include increasing the particle surface area available for dissolution by milling[4], improving the wettability with surfactants or doped crystals[5], decreasing crystallinity by preparing a solid dispersion[6], use of inclusion compounds such as cyclodextrin derivatives[7], use of polymorphic forms or solvated compounds[8], and use of salt forms.

Polyethylene glycols (PEGs) with molecular weights of 1,500-20,000 and various hydrophilic grades of gelucire are among the several carriers which have been employed in preparing solid dispersions. PEGs are widely used due to their low melting point, low toxicity, wide drug compatibility and hydrophilicity.[9] Solubility of PEGs in water is generally good, but it decreases with increase in their molecular weight.[10] The relatively low melting points of PEGs are advantageous for manufacturing of SDs using melting method. Furthermore, PEGs have the ability to solubilize some poor water soluble compounds and to improve their wettability.[11] The SDs of drugs with PEG 6000 may be useful to solve various problems such as stability, solubility, dissolution and bioavailability.[12]

Many researchers reported solid dispersions using Gelucire (polyglycolized glyceride) by fusion and solvent evaporation techniques.[13,14] Gelucire is a varying mixture of mono, di and triglycerides with polyethylene glycol esters of fatty acids. They are inert, semisolid and waxy amphiphilic excipients. A low hydrophilic-lipophilic balance (HLB) value in Gelucire decreases the dissolution rate whereas a high HLB value enhances the dissolution rate. The low HLB compounds

are composed of partial glycerides while those with HLB values above 10 are mixtures of partial saturated glycerides and polyethylene glycol (PEG) esters. Gelucire 44/14 is a semisolid excipient with an HLB value of 14 and melting point of 44^0C. Its hydrophilic property makes it a good choice for use as a carrier in preparation of solid dispersions by fusion method.[15] In this study, we prepared and characterized solid dispersions of glimepiride in PEG 6000, PEG10000 and Gelucire 44/14 varying compositions to improve solubility and dissolution rate. The solid dispersion exhibiting highest solubility and dissolution rate will be formulated into rapidly dissolving minitablet with more 85% drug dissolution in 30 min.

MATERIALS AND METHODS

Glimepiride was a gratis sample from Aurobindo Pharma Ltd, Hyderabad. Gelucire 44/14 was a gift sample from Gattefosse India Ltd, Mumbai. PEG 6000 and PEG 10000 were procured from Fine chemicals, Mumbai. All other chemicals and reagents used were of analytical grade.

Phase solubility study

Phase solubility studies were performed as per method described by Higuchi et al, 1965.[16] An excess amount of powdered glimepiride was placed in a screw-cap glass vial to which 20 mL of distilled water containing various concentrations (0, 0.5, 1, 2, 3, 4 and 5 % w/v) of carriers vis-a-vis PEG6000, PEG10000 and gelucire 44/14 (table 1). The samples were shaken at 37 ± 0.5°C for 72 h on a Remi mini rotary shaker-12R-DX. After 72 h of shaking, the samples were filtered through a 0.45µm membrane filter (Auroco, Thailand). The filtrate was diluted suitably and analyzed in an UV-Vis spectrophotometer UV-1800 (Shimadzu, Japan).

The value of the apparent stability constant, Ks for glimepiride-PEG6000, glimepiride-PEG10000 and glimepiride-gelucire 44/14 combinations was computed from the phase-solubility profiles, as described by

$$Ks = {Slope}/{Intercept\,(1 - Slope)} \quad (1)$$

The Gibb's free energy of transfer (ΔG_{tr}^0) of glimepiride from distilled water to solutions of carrier was calculated by using formula:

$$\Delta G_{tr}^0 = -2.303RT\left\{log\frac{S_0}{S_s}\right\} \quad (2)$$

Where S_0/S_s is the ratio of the molar solubility of glimepiride in distilled water of PEG6000, PEG10000 and gelucire 44/14 to that in the same medium.

FT-IR spectroscopy study

Glimepiride-carriers (1:1) interactions were assessed by FT-IR spectroscopy (IR-Affinity-1, Shimadzu, Japan). FT-IR spectra of pure drug glimepiride and its 1:1 solid dispersions with PEG6000, PEG10000 and gelucire 44/14 were recorded on IR using KBr discs. The instrument was operated under dry air purge and the scans were collected at a scanning speed of 2 mm/sec with resolution of 4 cm^{-1} over the region 4000-400 cm^{-1}. The FT-IR spectra are shown in table 3 and fig. 1.

Differential scanning calorimetry (DSC) study

The DSC measurements were performed on a DSC with thermal analyzer (DSC-60, Shimadzu, Japan). All the accurately weighed samples (about 2 mg) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10°C/min from 25 to 175°C. An empty aluminum pan was used as reference. DSC measurements were performed for glimepiride and its 1:1 solid dispersions with PEG6000, Peg10000 and gelucire 44/14 to study drug carrier interaction. The results are shown in fig. 2.

Preparation of Solid dispersions

Preparation of solid dispersions of Glimepiride with PEG6000, PEG10000 and Gelucire 44/14

Solid dispersions were prepared by fusion method. Glimepiride was added to the melt of PEG6000 maintaining a temperature of 50°C to obtain a clear molten mixture. The molten mixture was then added drop-wise to pre heated neusilin US2 with continued mixing. The solid dispersions were allowed to cool to room temperature by air-cooling followed by sieving through mesh 40. The compositions of solid dispersions are shown in table 2. Batch size of each formulation was 50g. PEG 10000 and gelucire 44/14 based solid dispersions of glimepiride were also prepared by similar method (table 2).

Solubility measurement of solid dispersions

Solubility of glimepiride and its solid dispersions was determined.[17] An excess amount of glimepiride and solid dispersions were added to 20 mL of freshly prepared distilled water in clean vials with continuous shaking on a Remi mini rotary shaker-12R-DX at 25 ± 0.5°C for 24h to achieve equilibrium. The filtered solutions were suitably diluted and analyzed spectrophotometrically. The results are shown in table 4.

Flowability and compressibility measurement

Solid dispersions were characterized for flow and compressibility by measuring Compressibility index (%), Hausner's ratio (H.R) and angle of repose (Θ).[18] The results are shown in table 3.

The Hausner's ratio is a number that is correlated to the flowability of powder. The Hausner's ratio is determined by following formula.

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density} \quad (3)$$

Compressibility index (CI) was determined according to the formula

$$C.I = \frac{(Tapped\ Density - Bulk\ Density)}{Tapped\ Density} \times 100 \quad (4)$$

Angle of repose was determined by allowing the solid dispersions to flow through a funnel (with a 10 mm orifice diameter) and measuring the angle between the horizontal and the slope of the heap of solid dispersions. The radius (r) and height (H) of the pile were measured. Then the angle of repose (θ) was calculated using following formula. The results are presented in table 4.

$$\theta = tan^{-1}\, {}^{h}/_{r} \qquad (5)$$

In-vitro dissolution test

The release of glimepiride from PEG6000, PEG10000 and gelucire 44/14 based solid dispersions was determined using USP paddle type Dissolution Tester at 50 rpm. Dissolution was examined using 900 mL of simulated intestinal fluid (SIF) without enzyme. The temperature was maintained at 37 ± 0.2°C. Samples each containing 5 mL were withdrawn at 5, 10, 15, 30, 45 and and 60 min intervals, filtered through a Whatman filter of 0.45 µm and replaced with an equal amount of fresh dissolution medium to maintain sink condition. Samples were then suitably diluted and analyzed spectrophotometrically at 226 nm. The dissolution studies were conducted in triplicate. The dissolution profiles were evaluated for amount of drug released in initial 30 min (Q_{30} min) and time taken to release 50% of the drug (T_{50}).

Preparation of rapidly dissolving minitablets

The solid dispersion exhibiting highest solubility and dissolution rate among all the three carriers were formulated as rapidly dissolving minitablets. The selected solid dispersions were mixed with superdisintegrant sodium starch glycolate (SSG) in various proportions. Lactose was added as diluent. There was no need to add any lubricant as neusilin US2 improved the flowability of solid dispersions to the desired level. One minitablet was also formulated without using superdisintegrant SSG (F10). The minitablets were compressed on a multistation tablet press (Karnavati MiniPress II, Ahmedabad) with a flat, circular multitip punch of 3 mm diameter to produce glimepiride rapidly dissolving minitablets. The composition is shown in table 5.

Quality Control tests for minitablets

The prepared minitablets were subjected to standard quality control tests. Weight variation was determined by weighing 20 tablets individually, the average weight was calculated and the percentage variation of each tablet was determined. Hardness was determined by testing 6 tablets from each formulation using a Electrolab digital portable hardness tester EH-01 (Electrolab, India) and the average applied pressure (kg/cm^2) required to crush each tablet was determined. Friability was determined by firstly weighing 10 tablets then placing them in a friability tester EF-2W (Electrolab, India) which was rotated for 4 min at 25 rpm. After dusting, the total remaining weight of the tablets was recorded and the percentage of friability was calculated. The disintegration time for the tablets was determined in 900 mL of distilled water using a programmable tablet disintegration tester ED-2L (Electrolab, India). The results are shown in table 6. In vitro dissolution study was performed for the minitablets in a similar manner as described for solid dispersions.

Dissolution Efficiency

The percent dissolution efficiency (% DE) was computed to compare the relative performance of various formulations. The % DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, *t*, expressed as a percentage of the area of the rectangle described by 100% dissolution at the same time.[19] The % DE can be calculated from the following equation

$$\%\, DE = \frac{\int_0^t Y dt}{Y_{100} t} \qquad (6)$$

Where, *Y* is the percent drug dissolved at time *t*.

Hixson Crowell Cube root law

Finally Hixson and Crowell's cubic root law of dissolution was applied to evaluate the effect of change in surface area on dissolution rate of all the formulations. The dissolution data of glimepiride and IR tablets were analyzed as per Hixson-Crowell's cube root equation. Hixson-Crowell introduced the concept of changing surface area during dissolution and derived the "cube-root law" to nullify the effect of changing surface area and to linearize the dissolution curves. Hixson-Crowell's cube root law is given by the following equation. The results are shown in table 7.

$$(W_0)^{1/3} - (W_t)^{1/3} = Kt \qquad (7)$$

Where W_0 is initial mass and W_t is the mass remained at time 't', K is Hixson Crowell cube root constant.

RESULTS AND DISCUSSION

Phase solubility study

The solubility of glimepiride in water at 25°C is 0.035 mg/mL therefore it can be considered as a poorly water soluble drug. The phase solubility data for glimepiride in all the 3 carriers PEG6000, PEG10000 and gelucire 44/14 are presented in table 1. From this table, it can be seen that the apparent solubility of glimepiride increased with increase in the concentration of carriers. At the highest carrier concentration (5% w/w), the solubility increased approximately 10-fold, 17 fold and 28 fold for PEG6000, PEG10000 and gelucire 44/14 respectively at 25°C. An indication of the process of transfer of glimepiride from pure water to aqueous solution of carriers was obtained from the values of Gibbs free energy change. The obtained values of ΔG_{tr}° are shown in table 1. The ΔG_{tr}° values shows whether the reaction condition is favorable or unfavorable for drug solubilization in the aqueous carrier solution. Negative ΔG_{tr}° values indicate favorable conditions. ΔG_{tr}° values were all negative for all the 3 carriers PEG6000, PEG10000 and gelucire 44/14 at various concentrations,

indicating the spontaneous nature of glimepiride solubilization, and decreased with an increase in carrier concentration, demonstrating that the reaction became more favorable as the concentration of carrier increased. These values also indicated that the extent of improvement in solubility was more with gelucire 44/14 as compared with both grades of PEG.

Table 1: Effect of Concentration of carriers (PEG6000, PEG10000 and Gelucire 44/14) on Gibbs free energy

Concentration of carrier (% w/v)	Solubility (mg/mL)			ΔG_{tr}° (J/mol)*		
	PEG6000	PEG10000	Gelucire 44/14	PEG6000	PEG10000	Gelucire 44/14
0	0.035	0.356	0.352	0	0	0
0.5	0.16	0.24	0.37	-2.435	-4.217	-.8.751
1	0.2	0.28	0.54	-3.598	-6.341	-10.324
2	0.24	0.32	0.61	-6.367	-8.234	-11.387
5	0.29	0.46	0.72	-7.267	-10.502	-14.214
4	0.33	0.51	0.86	-9.128	-11. 343	-16.398
5	0.37	0.59	0.97	-10.456	-14.236	-19.435

Fourier Transform Infrared (FT-IR) Spectroscopy

FT-IR spectrum of glimepiride (fig. 1A) is characterized by the absorption of carbonyl (C=O) group at 1707.66 cm^{-1}. It also contains NH group as it showed absorption band at 3388.07 and 3288.04 cm^{-1}. The sulphonyl group bands are located at 1346.07 and 1152.26 cm^{-1} for pure glimepiride. The absorption band at 1275.68 cm^{-1} corresponds to C-N stretching vibrations. The band at 1543.74 cm^{-1} indicated the presence of C=C. The absorption band for C-H was found at 2931 cm^{-1}. All the peaks were retained in all solid dispersions with PEG6000 (fig. 1B), PEG10000 (fig. 1C) and gelucire 44/14 (fig. 1D). The results of FT-IR spectroscopy are summarized in table 3.

Table 3: FT-IR data of pure drug Glimepiride and its solid dispersions

Functional group	Glimepiride	SD of Glimepiride: PEG6000: Neusilin US2 (1:1:0.5)	SD of Glimepiride: PEG10000: Neusilin US2 (1:1:0.5)	SD of Glimepiride: Gelucire 44/14: Neusilin US2 (1:1:0.5)
NH group	3388.07 and 3288.04	3389.03 and 3288.04	3369.03 and 3288.04	3387.03 and 3288.01
C-H	2931	2885.95	2884.02	2932
Carbonyl (C=O) group	1707.66	1707.66	1707.66	1706.41
C=C	1543.74	1543.74	1543.70	1544.32
Sulphonyl group	1346.07	1342.21	1345.11	1347.09
C-N stretching vibrations	1275.68	1279.54	1278.57	1274.65

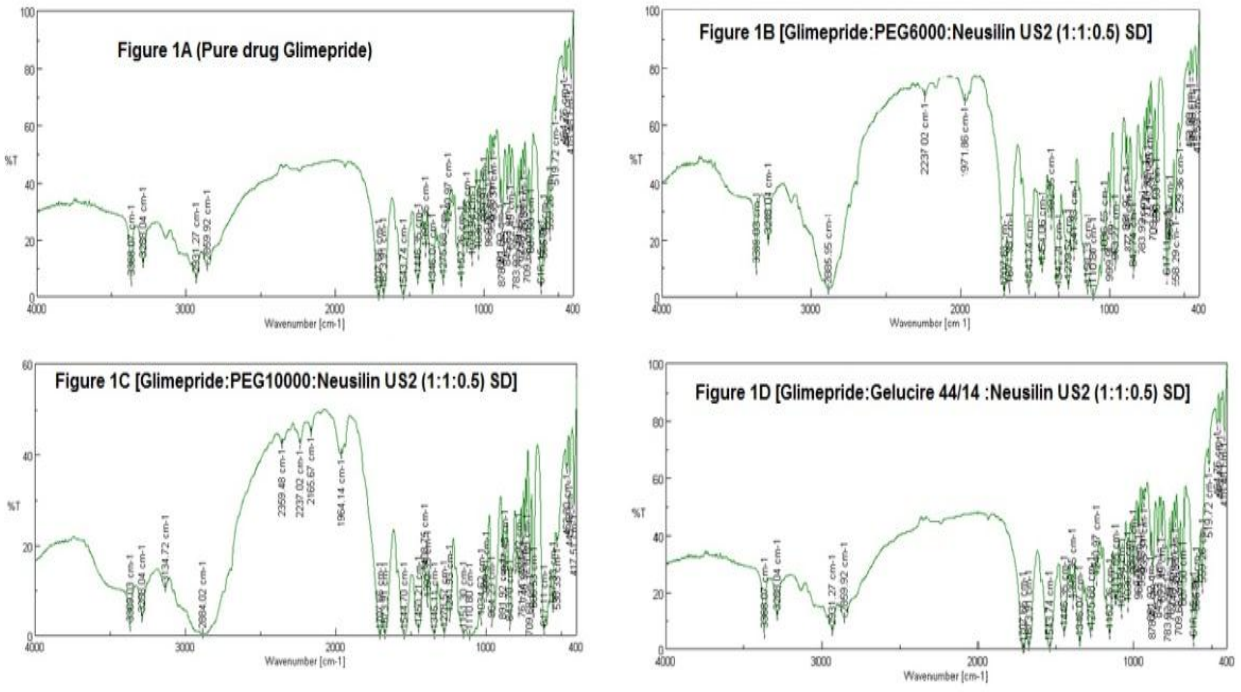

Fig. 1: FT-IR spectrum of glimepiride and other solid dispersions.

Differential Scanning Calorimetry

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). The thermal behavior of glimepiride and its solid dispersions with PEG6000, PEG10000 and gelucire 44/14 along with neusilin US2 was studied by DSC. The DSC thermogram of pure glimepiride is shown in figure 2A. The glimepiride showed a sharp melting peak at 210^0C indicates that it is a pure and crystalline drug substance. The DSC thermogram of soild dispersion with all the 3 carriers showed a sharp peak at 54^0C, 62^0C and 45^0C for PEG6000, PEG10000 and gelucire 44/14 respectively (fig. 2B to 2D). Solid dispersions exhibited a single endothermic peak for carrier whereas all solid dispersions corresponding to the fusion of the carrier no peak was present associated to the melting of the drug. We can hypothesize that during the scanning of the temperature the solid drug (when present) dissolves into the molten carrier starting from the melting of the carrier (around 45^0C) and is no more present in its undissolved form inside the systems, when the melting temperature of glimepiride is reached.[20] Hence there is no interaction between the carriers and glimepiride used in the present research.

In order to achieve more than 85% drug release in 30 min solid dispersions were prepared using PEG6000, PEG10000 and gelucire 44/14 in various drug to carrier ratios such as 1:1. 1:3 and 1:5. (table 2).

Table 2: Composition Glimepride solid dispersions

Formulation Code	Glimepiride	PEG 6000	PEG10000	Gelucire 44/14	Neusilin US2
F1	1	1	-	-	0.5
F2	1	3	-	-	1.5
F3	1	5	-	-	2.5
F4	1	-	1	-	0.5
F5	1	-	3	-	1.5
F6	1	-	5	-	2.5
F7	1	-	-	1	0.5
F8	1	-	-	3	1.5
F9	1	-	-	5	2.5

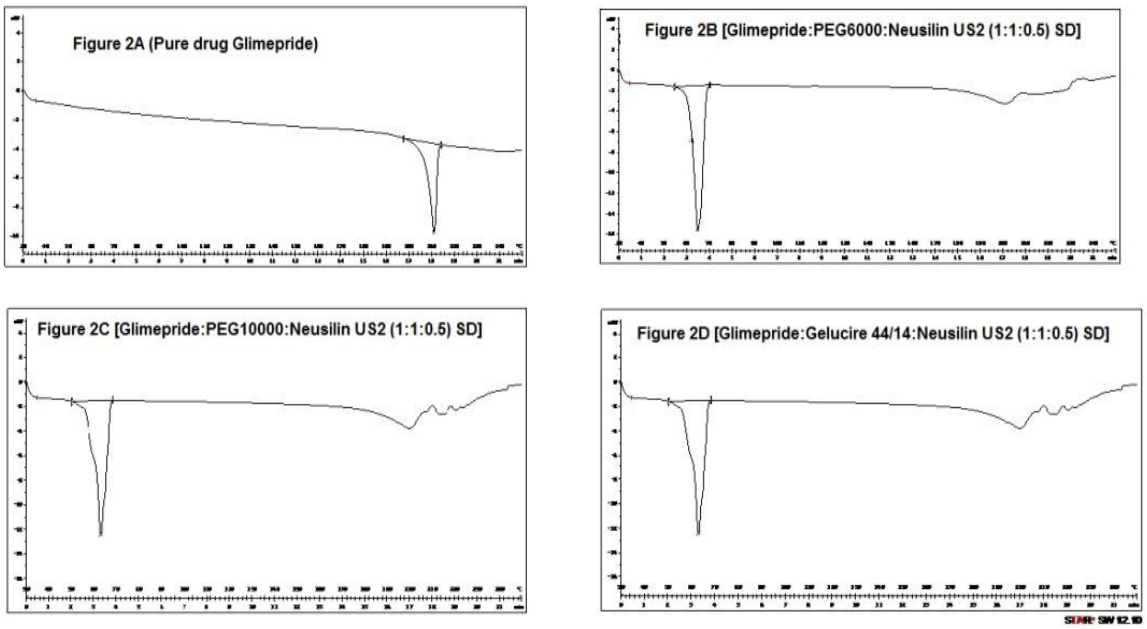

Fig. 2: The DSC thermogram of pure glimepiride and solid dispersions.

Solubility Study

Solubility of pure drug glimepiride and its solid dispersions with various carriers were determined and presented in table 4 and fig. 3. From the solubility study, we can infer that as the proportion of hydrophilic carrier increased solubility of glimepiride also increased. In case of PEG6000, PEG10000 and gelucire 44/14 based solid dispersions 8, 21 and 23 times improvement in solubility was observed with the highest ratio drug to carrier (1:5). The improved solubility of glimepiride in solid dispersions can be explained by the improved wettability of the glimepiride particles in aqueous solution from all the 3 carriers.[21]

Table 4: Solubility and micromeritic properties of Glimepride and its solid dispersions.

Formulations	Solubility (µg/mL)	Angle of repose (^{0})*	Compressibility Index (%)*	Hausner's ratio*
Glimepride	35 ± 3	44 ± 3	32 ± 1.5	1.42 ± 0.4
F1	160 ± 15	29 ± 3	21 ± 2	1.24 ± 0.3
F2	240 ± 13	25 ± 2	18 ± 1	1.32 ±0.3
F3	290 ± 14	24 ± 1	17 ± 2	1.21 ±0.3
F4	284 ± 13	21 ± 4	19 ± 2	1.19 ±0.2
F5	569 ± 14	24 ± 1	18 ± 1	1.22 ± 0.1
F6	735 ± 16	22 ± 2	18 ± 2	1.23 ±0.1
F7	405 ± 18	23 ± 2	19 ± 2	1.24 ±0.8
F8	768 ± 12	23 ± 3	18 ± 1	1.21 ±0.5
F9	802 ± 16	25 ± 3	19 ± 2	1.23 ±0.4

Mean ± SD, n =6

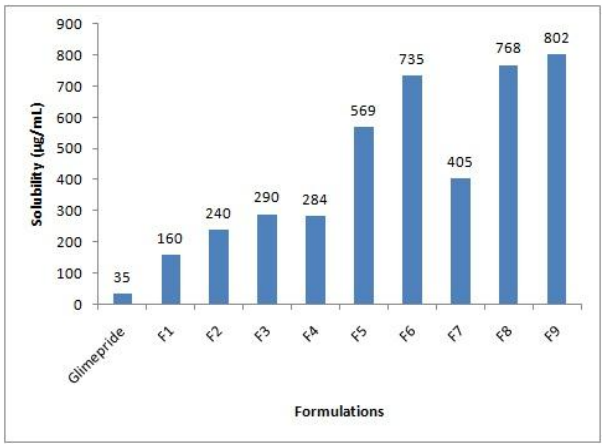

Fig. 3: Solubility of pure drug glimepiride and its solid dispersions with various carriers

Flowability and compressibility

The values of angle of repose, Carr's index (C.I) and Hausner's ratio (H.R) for drug powder glimepiride reveals that it is a poorly flowable drug. All the nine solid dispersions showed significant improvement in flowability and compressibility suggesting their suitability for tablet formulation. Some trial soild dispersions prepared without neusilin US2 showed stickiness. Addition of Neusilin US2 (50% of the quantity of carriers) in each solid dispersion formulation was found to be optimal for converting the waxy dispersion into flowable powder. These powder formulations could be processed into a tablet. This was attributed to the high oil adsorption capacity and high specific surface area of neusilin US2.[22]

In-vitro Dissolution studies

The dissolution profile of glimepiride and its solid dispersions with PEG6000, PEG10000 and gelucire 44/14 are shown in figure 4. In vitro dissolution studies for the pure drug glimepiride showed nearly 20% drug dissolution within 60 min. This can be attributed to its poor solubility. In case of PEG6000 based solid dispersions (F1-F3) improvement in dissolution rate was observed with increase in the ratio of carrier (fig. 4A). This can be attributed to the uniform and homogenous distribution of glimepiride in the PEG6000 crust in a highly dispersed state as a result of melt in procedure. Complete homogenous inclusion of the glimepiride particles in the carrier matrix was achieved by incorporating the drug in the melted PEG-6000 with gentle mixing. Thus, when a binary system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug into fine particles, which increase the available dissolution surface.[23] In case of formulation F3 around 60% of drug dissolved within 30 min of dissolution study. The dissolution profile of PEG10000 based solid dispersions (F4-F6) are shown in figure 4B. At the same drug to carrier ratios, PEG10000 based solid dispersions exhibited better dissolution. Lower hydrophilicity of PEG 6000 compared to PEG 10000 might be the main cause of its lesser drug solution. Therefore, the dissolution rate enhancement of poorly soluble drugs from SDs seems to be affected by various factors, including the hydrophilicity of soluble carrier and the viscosity of the medium around the particles.[24] It was also observed that when the ratio of PEG10000 increased from 1:1 (F4) to 1:3 (F5) dissolution rate increased but further increase from 1:3 (F5) to 1:5 (F6) did not show any significant additional improvement in dissolution. The dissolution profile is shown in figure 4B. Increasing the PEG10000 concentration in solid dispersion formulations only to a specific amount resulted in better drug dissolution and further increasing the ratio of PEG10000 did not show any additional improvement. This might be attributed to the viscous layer formed around the solid particles due to higher PEG10000 concentrations.[25] Formulation F5 and F6 showed around 75 to 80% drug dissolution within 30 min. The dissolution profile of gelucire 44/14 based solid dispersions (F7-F9) are shown in figure 4C. It was observed that as the proportion of carrier increased dissolution rate increased. This can be attributed to the absence of crystalline structure, surfactant properties and improved wettability of the drug particles in the form of dispersion.[20] Gelucire 44/14 has an HLB value of 14 and is expected to solubilize the hydrophobic glimepiride in solid state. Both solid dispersion formulations F8 and F9 exhibited more than 85% drug dissolution within 30 min.

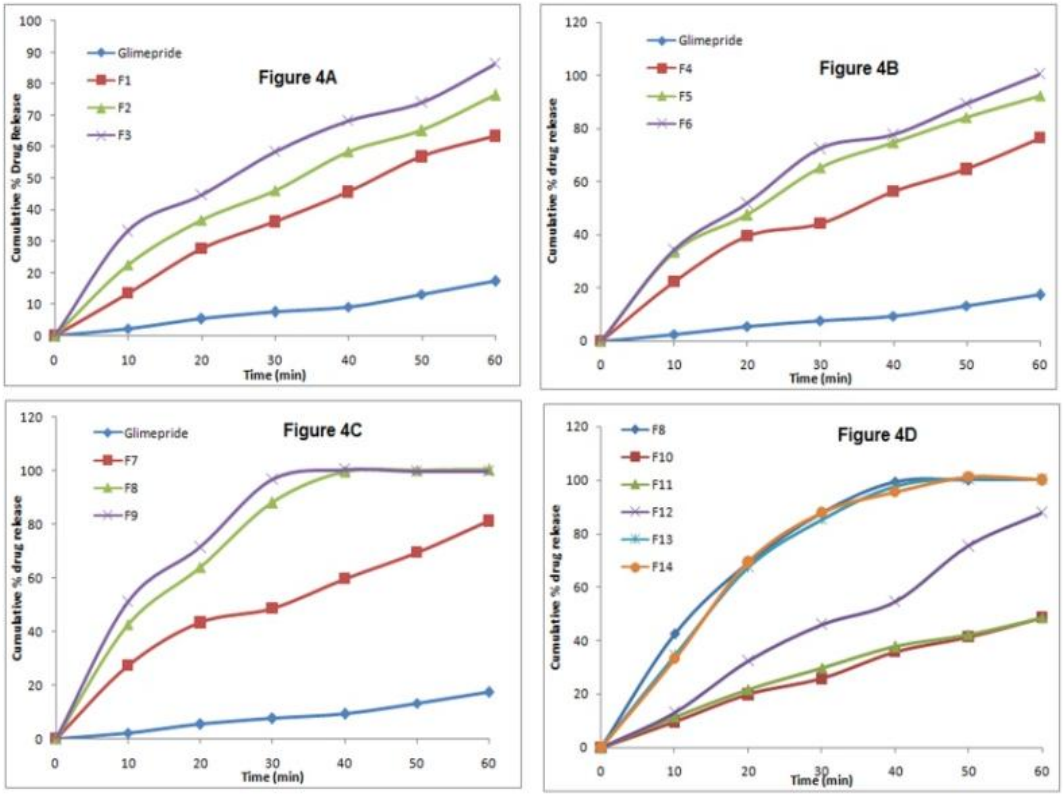

Fig. 4: The dissolution profile of glimepiride and its solid dispersions.

Preparation of Minitablets

The solid dispersions prepared with different carriers such as PEG6000, PEG10000 and gelucire 44/14 were screened for further formulation into a rapidly dissolving tablet. In case of gelucire 44/14 based solid dispersions, highest dissolution was observed. As both formulation F8 and F9 showed more than 85 % of drug dissolution within 30 min, solid dispersion formulation F8 was selected for further formulation into a rapidly dissolving tablet keeping in view the minimum quantity of carrier. As the dose of glimepiride is very low (2 mg) it was decided to compress this into a minitablet so that it can be prepared with minimum quantity of excipients. One formulation was compressed without any superdisintegrant (F10). Sodium starch glycolate was added as a superdisintegrant in different percentages 0.25, 0.5, 0.75 and 1% to minitablet formulations (F11-F14) (table 5).

Table 5: Composition of Glimepride minitablets.

Formulations	Solid dispersion (F8)			Sodium starch glycolate	Lactose	Total
	Glimepride	Gelucire 44/14	Neusilin US2			
F10	2	6	3	0	9	20 mg
F11	2	6	3	0.5	8.5	20 mg
F12	2	6	3	1	8	20 mg
F13	2	6	3	1.5	7.5	20 mg
F14	2	6	3	2	7	20 mg

Quality Control Tests for Minitablets

Drug content values (97-100 %) ensured uniform mixing of glimepiride, gelucire 44/14, neusilin US2, sodium starch glycolate and lactose. Hardness of the mini tablets was in the range of 4.9 to 6.1 kg/cm^2. This revealed that the required compressibility was imparted by neusilin US2. Gelucire 44/14 was a waxy material; tend to stick to the punches during compression. This problem was also solved by mixing with porous carrier neusilin US2. Friability values were in the range of 0.21 and 0.87 %, which ensured no loss of material from the surface or edge of mini tablets. This may be attributed to the waxy nature of carriers. All the formulations passed weight variation test which was an indication of good flowability. Formulation F10 showed a longer disintegration time of 34 min which can be attributed to absence of disintegrant. As the proportion of sodium starch glycolate increased (F11 to F14), the disintegration time of minitablets decreased from 21 to 3 min. This was due to rapid swelling of SSG.[26] The results of evaluation tests are summarized in table 6.

Table 6: Quality Control Tests of Glimepride minitablets.

Formulation code	Hardness (Kg/cm^2)*	D.T. (min)*	Friability (%)*	Weight Variation	Drug Content (%)*
F10	6.1 ± 0.31	34 ± 0.2	0.47	PASS	98.9 ± 1.6
F11	5.4 ± 0.21	21 ± 0.3	0.28	PASS	97.4 ± 2.2
F12	4.9 ± 0.89	13 ± 0. 3	0.87	PASS	99.6 ± 3.1
F13	5.6 ± 0.32	2.6 ± 0.3	0.21	PASS	97.8 ± 1.2
F14	5.5 ± 0.19	1.9 ± 0. 3	0.49	PASS	98.2 ± 3.1

* Mean ± SD, n=6

In Vitro Dissolution for Minitablets

The dissolution profile of minitablets is shown in figure 4D. The composition of formulation F8 and F10 are same except lactose which was incorporated in minitablet formulation (F10). Solid dispersion (F8) showed an excellent dissolution rate of more 85% in 30 min. But when the same formulation was compressed into a minitablet a significant decrease in dissolution rate was observed due to slower disintegration of minitablets of 34 min. This led to reduced surface area to dissolution medium. Incase formulation F10, nearly 25% of drug dissolved in 30 min. The dissolution rate decreased from 85 to 25 % at 30 min. Incorporation of sodium starch glycolate decreased the disintegration time and also increased the dissolution rate.

Both minitablet formulation (F13 and F14) showed more than 85% dissolution at 30 min. Hence minitablets were subjected to evaluation of dissolution related parameters.

The dissolution efficiency (DE_{30}), percent drug dissolved in 30 min (Q_{30}) and time at which 50% of drug dissolved (T_{50}) were determined for optimized solid dispersion (F8) and minitablets (F10-F14). The DE_{30} value for each formulation is presented in table 7. The DE_{30} value for pure drug glimepiridewas significantly lower than solid dispersions and rapidly dissolving minitablets. Formulation F8 showed very high dissolution efficiency (91) however when the same formulation was compressed into a tablet (F10), the dissolution efficiency decreased to 28. Addition of SSG at 0.75% increased dissolution efficiency. Q_{30} values for formulation F13 showed more than 10 fold increase in dissolution rate compared to glimepride. Similarly T_{50} values for pure drug glimepiridecould not be determined as only 17 % of drug dissolved in 1 h of dissolution study. Lowest time of T_{50} was observed for F13 indicating higher dissolution potential of gelucire 44/14 based rapidly dissolving minitablet. Correlation coefficient for Hixson Crowell's equation was higher for solid dispersion (F8), F13 and F14 formulations suggesting that the rate of dissolution increased with increase in surface area.

Table 7: Dissolution parameters of Glimepride minitablets

Formulation	% DE_{30}	Q_{30}	T_{50} (min)	Hixson Crowell's cube root constant (r^2)
Glimepride	8.7	8	*	0.871
F8	91	87	17	0.997
F10	28	25	60	0.865
F11	32	29	60	0.912
F12	47	45	35	0.932
F13	86	85	15	0.996
F14	87	87	14	0.998

% DE_{30} is the percent dissolution efficiency at 30 min, Q_{30} Percent of drug dissolved in 30 min, *50 % of drug was not dissolved within 1 h of dissolution study.

CONCLUSION

Hence from the above research work, it may be concluded that PEG6000, PEG10000 and gelucire 44/14 can be used to enhance the dissolution of a poorly water soluble drug glimepride. Gelucire 44/14 showed higher solubility and dissolution rate enhancement potential. The surface adsorbent, Neuslin US2 may be used to impart good flow and compressibility to solid dispersions. Presence of sodium starch glycolate as superdisintegrant also contributed significantly in dissolution enhancement of drug. The rapidly dissolving minitablets of glimepiridewere prepared successfully with a dissolution rate of more than 85% in 30 min.

ACKNOWLEDGMENT

Authors are gratefully acknowledging the support provided by the School of Pharmaceutical education and Research, Behampur University, Berhampur, Ganjam, Odisha, India and Institute of Pharmacy and Technology, Salepur, Cuttack, Odisha, India.

CONFLICT OF INTERESTS

Authors declare that they have no conflict of interest.

REFERENCES

1. Kouichi I, Masaki W, Youhei N, Takahiro S, Nobuki T, Masahiko T. Efficacy of glimepiride in Japanese type 2 diabetic subjects. Diab Res Clin Pract, 2005; 68: 250-257.
2. Geinsen K. Special pharmacology of the new sulfonylurea glimepiride. Drug Res., 1988; 38: 1120-1130.
3. Frick A, Moller H, Wirbitzki E. Biopharmaceutical characterization of oral immediate release drug products. In vitro/in vivo comparison of phenoxymethylpenicillin potassium, glimepiride and levofloxacin. Eur J Pharm Biopharm, 1998; 46: 305-311.
4. Habib FS, Attia MA. Effect of particle size on the dissolution rate of monophenylbutazone solid dispersion in presence of certain additives. Drug Dev Ind Pharm., 1985; 1: 2009-2019.
5. Chow AHL, Hsia CK, Gordon JD, Young JWM, Vargha-Butler EI. Assessment of wettability and its relationship to the intrinsic dissolution rate of doped phenytoin crystals. Int J Pharm., 1995; 126: 21-28.
6. Flego C, Lovrecich M, Rubessa F. Dissolution rate of griseofulvin from solid dispersion with poly(vinylmethylether: maleic anhydride). Drug Dev Ind Pharm., 1988; 14: 1185-1202.
7. Pitha J. Amorphous water-soluble derivatives of cyclodextrins: nontoxic dissolution enhancing excipients. J Pharm Sci, 1985; 74: 987-990.
8. Sekiguchi K, Kanke M, Tsuda Y, Ishida K, Tsuda T. Dissolution behavior of solid drugs. III. Determination of the transition temperature between the hydrate and anhydrous forms of phenobarbital by measuring their dissolution rates. Chem Pharm Bull, 1973; 21: 1592-1600.
9. Dennis A, Farr S, Kellaway I, Taylor GDR. In-vivo evaluation of rapid release and sustained release Gelucire capsule formulations. Int J Pharm, 1990; 65: 85-100.
10. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm, 2000; 50: 47-60.
11. Betageri G, Makarla K. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int J Pharm, 1995; 126: 155-160.
12. Tashtoush BM, Al-Qashi ZS, Najib NM. In-vitro and in-vivo evaluation of glibenclamide in solid dispersion systems. Drug Dev Ind Pharm, 2004; 30: 601-607.
13. Damian F, Blaton N, Naesens L, Balzarini J, Kinget R, Augustijns P. Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. Eur J Pharm Sci., 2000; 10: 311-322.
14. Fattah AAM, Bhargava HN. Preparation and in vitro evaluation of solid dispersions of halofantrine. Int J Pharm, 2002; 235: 17-33.
15. Dordunoo SK, Ford JL, Rubinstein MH. Solidification studies of polyethylene glycols, gelucire 44/14 or their dispersions with triamterene or temazepam. J Pharm Pharmacol, 1996; 48: 782-789.
16. Higuchi T, Connors K. Phase-solubility techniques. Adv Anal Chem Instrum, 1965; 4: 117-123.
17. Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of Nifedipine. Int J Pharm., 2005; 99: 167-177.
18. Wells JI, Aulton ME. Pharmaceutical Preformulation. In: M.E. Aulton, editor, Aulton's pharmaceutics. The design and manufacture of medicines. Hungary. Elsevier, 2007; 355-357.
19. Khan CA, Rhodes CT. The concept of dissolution efficiency. J Pharm Pharmacol, 1975; 27: 48-49.
20. Adamo F, Jose RM, Juan MG, Jose IP, Antonio MR. Diclofenac salts, II. Solid dispersions in PEG6000 and Gelucire 50/13. Eur J Pharm Biopharm, 2005; 60: 99-111.
21. Potluri RHK, Bandari S, Jukanti R, Prabhakar R, Veerareddy PR. Solubility enhancement and physicochemical characterization of carvedilol solid dispersion with Gelucire 50/13. Arch Pharm Res., 2011; 34 (1): 51-57.
22. Sruti J, Patra CN, Palatasingh HR, Swain SK, Beg S, Dinda SC, Rao MEB. Improvement in dissolution rate of cefuroxime axetil by using Poloxamer 188 and Neusilin US2. Ind J Pharm Sci., 2013; 75(1): 65-73.
23. Samar Afifi. Solid dispersion approach improving dissolution rate of stiripentol: a Novel Antiepileptic Drug. Iran J Pharm Res., 2015; 14 (4): 1001-1014.
24. Bolourchiana M, Mehdi M, Simin D. The effect of PEG molecular weights on dissolution behavior of simvastatin in solid dispersions. Noushin Iran J Pharm Res., 2013; 12: 11-20.
25. Khan GM, Jiabi Z. Preparation, characterization and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (PEG), talc and PEG-talc as dispersion carriers. Drug Dev Ind Pharm, 1998; 24(5): 455-462.
26. Patra CN, Swain S, Mahanty S, Panigrahi KC. Design and characterization of aceclofenac and paracetamol spherical crystals and their tableting properties. Powder Technology, 2015; 274: 446-454.