Research Article

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Optimizing surfactant ratio for the production of capsules containing glicazide using solid dispersion technique

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Abstract

The objective of this study was to formulate and prepare gliclazide capsule by solid dispersion method using different surfactants and their in vitro evaluation. Solubilising capacity of polyethylene glycol (PEG 6000, PEG 20000) and polyvinylpyrrolidone (PVP K 30) was determined at 2% concentration where gliclazide was used as a model drug and water was used as control for comparison. Results showed that PVP K 30 exhibited maximum solubilising capacity. Fusion method of solid dispersion was adopted for preparation of capsules using PEG 6000 & PEG 20000 in different ratios. Although these agents are claimed to be good surfactants but our results showed that, the highest cumulative drug release was 1.81 % for gliclazide and PEG 6000 in a ratio of 1:6. The flow property of capsule granules was determined by angle of repose. The capsules were also subjected to weight uniformity test, disintegration test and moisture permeation test and the chemical analysis of solid dispersions were done by FTIR. From this study, it can be concluded that it is possible to formulate and prepare gliclazide capsule by using solid dispersion method.

Keywords: Gliclazide, Solid dispersion, Surfactants, In vitro evaluation, Solubilising capacity, Fusion method, Different ratios.

Introduction

In every 10 seconds, one person in the world passes away because of ignorance about diabetes and ways to control it [1, 2]. Diabetes is a metabolic disorder, it happens because of dysfunction of insulin which regulates blood sugar.

Sulfonylureas are the oldest class of oral anti-hyperglycemic agents available for the treatment of type 2 diabetes. Gliclazide is a second generation hypoglycemic sulfonylurea, which is useful in the treatment of type 2 diabetes [3]. Following oral administration, however, gliclazide exhibits slow rate of absorption and inter individual variation in bioavailability. Stated problems of gliclazide might be due to its poor water solubility and slow dissolution rate [4, 5].

Depending upon the large number of patients, medication has to be up-dated. Again, the number of diabetic patients in this world is increasing day by day. Therefore preparations containing anti-diabetic drug(s) should be investigated with more effort for the benefit(s) of mankind. Thus, the objective of this study was to optimize the surfactant ratio for production of gliclazide capsule using solid dispersion technique, which is an anti-diabetic drug. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate. Since the 1960s, many solid-dispersion formulations have been developed. Solid dispersions are prepared by various methods like fusion process, solvent process, fusion solvent process and supercritical fluid process [6]. Solid dispersions must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization [7].

Gliclazide is a type 2 anti-diabetic drug. The oral route of drug administration is the most important route of administering drug for systemic effects. The dissolution of administered drug in the solid state is a prerequisite for efficient subsequent transport within the human body which control the drug bioavailability as well as therapeutic efficacy. The aim of the study of formulation and preparation of gliclazide by solid dispersion for treatment of type 2 diabetes mellitus. An attempt was made to formulate and develop by solid dispersion: to formulate the drug in a capsule form by solid dispersion systems and to improve the bioavailability of gliclazide by solid dispersion method as it is a poorly water soluble drug.

Materials and Methods

Materials

Gliclazide was received as gift from Square Pharmaceuticals Ltd. Polyethyleneglycol (PEG 6000 and 20000) and polyvinylpyrrolidone (PVP K 30) were purchased from Merck, Germany. All ingredients used were of analytical grade.

Preparation of solid dispersions (SDs) using melting or fusion method

Solid dispersions of gliclazide as shown in table 1 were prepared by melting or fusion method as described by Kulkarni et al. [8]. Where polymers was placed in a beaker and allowed to melt by indirect heating up to 65° C. To the molten mass, an appropriate amount of gliclazide was added and stirred constantly until a homogenous dispersion was obtained. The mixture was then cooled rapidly by placing the beaker in an ice bath. The mass was solidify and then powdered in a mortar and was sieved through an 18-mesh screen.

Table 1: Composition of solid dispersions of gliclazide

Formulation code	Drug : Polymer	Ratio
F1	Gliclazide : PEG 6000	1:11
F2	Gliclazide : PEG 6000	1:20
F3	Gliclazide : PEG 6000	1:40
F4	Gliclazide : PEG 20000	1:11
F5	Gliclazide : PEG6000	1:6
F6	Gliclazide : PEG 6000	1:10
F7	Gliclazide : PEG 6000 : PEG 20000	1:3:3
F8	Gliclazide : Lactose	1:6

Preparation of gliclazide capsule

Gliclazide capsules were prepared by hand filling. Each capsule contained 30 mg of gliclazide.

Preparation of phosphate buffer solution @ pH 7.4

Phosphate buffer solution @ pH 7.4 prepared by the method as described by Robert, 1986-1987 [9].

Property evaluation

Preliminary investigation on solubility of gliclazide

The preliminary investigation on solubility of gliclazide was conducted at normal day temperature where gliclazide (100 mg) was mixed with aqueous surfactant solution (2 %, 5 mL) for 72 hrs by using mechanical shakers at a slow rpm. At the end of 72 hrs period, the supernatant was collected and was filtered through "Double Rings" filter paper. The filtrate was collected and suitably diluted with a mixture of methanol & water in the ratio of 50:50. The drug content was estimated spectrophotometrically at a wavelength of 235 nm [10].

Angle of repose

Before making the capsules, angle of repose of granules was calculated to determine the flow property of granules. The accurately weighed granules were taken in a funnel. The height of funnel was adjusted by a stand in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through the funnel freely on to the surface [11]. The diameter of the granules cone was measured by a scale and the angle of repose was calculated using the following equation:

$$\text{Angle of repose, } \emptyset = \tan^{-1} h/r$$

Here, H= Height of granules cone, R= Radius of granules cone

Weight uniformity test after filling the capsule

Six capsule shells were individually weighted in Electronic balance (Shimadzu Corporation, Japan). The shells then filled with contents, weighed and the net weight of the contents calculated by subtraction. From the results of an assay, the weight of the contents for each individual capsule is determined and compared with the average weight of contents. The capsules passed the test, as the weight of individual capsule weight fall within (90-110) % of the average weight [11].

Disintegration test studies

Disintegration test was performed by using disintegration tester (Campbell Electronics, India). For performing disintegration test one capsule was put in each tube. The disintegration medium was distilled water at 37°C. To fully satisfy the test, the capsules disintegrate completely into a soft mass within 30 minute having no palpably firm core and only some fragments of the gelatin shell [11].

Dissolution studies

Dissolution studies of Gliclazide in solid dispersions were performed by using tablet dissolution test apparatus-2 (6+2 station, Veego, India). The paddle rotation speed was 100 rpm. The apparatus was filled with 900 ml distilled water and temperature was maintained at 37±0.5°C. The Solid dispersion equivalent to 30 mg of gliclazide capsule was added into the dissolution medium using capsule bucket. At 10 min, 20 min, 30 min, 1 hr, 2hr & 3 hr intervals, 10 ml samples were withdrawn, filtered through "Double Rings" filter paper and assayed by UV-visible spectrophotometer (Shimadzu UV-1601) at 235 nm wavelength. Fresh medium (10 ml) was added to the dissolution medium after each sampling to maintain a constant volume throughout the test [12].

Moisture permeation test

The degree and rate of moisture penetration is determined by packaging the dosage unit (30 capsules) with color revealing desiccant pellet. The packaging unit then exposed to known relative humidity over a specified time and observed the desiccant pellet for color change and compared the pre-and post-weight of the packaged unit. Amber glass bottles were used for this technique. The bottles were air tight by para film and the test was done after 7 days by using the following equation-

$$\% \text{ of moisture absorption} = \frac{\text{pre wt capsules-post wt capsules}}{\text{pre wt capsules}} \text{ X } 100$$

Chemical analysis on solid dispersions

Fourier transforms infrared (FTIR) spectroscopy

Fourier transform infrared (FTIR) spectra were recorded using FTIR spectrophotometer (IR prestige- 21, Shimadzu). The samples (Gliclazide, SDs ratio at 1:20, PM- water, PM- Abs. and PEG 6000) were previously ground and mixed thoroughly with potassium bromide (an infrared transparent matrix) in a ratio of 1:100. The KBr discs were prepared by compressing the powders at a pressure of 6 tons for 5 min in a hydraulic press (Shimadzu, Japan). Thirty eight scans were obtained at a resolution of $2cm^{-1}$, from 4000 to 500 cm^{-1}.

Results and Discussion

Preliminary investigation on solubility of gliclazide

Solubilizing capacity of PEG 6000, PEG 20000 and PVP K30 was determined at 2 % concentration, where gliclazide was used as drug and water was used as control for comparison. Results showed that, the amount of gliclazide solubilised in the surfactant solutions were higher than water (fig. 1). In PVP K 30 it was the

highest & in PEG 6000 it was second highest. So attention was focused on using these surfactants in the preparation of solid dispersions of gliclazide.

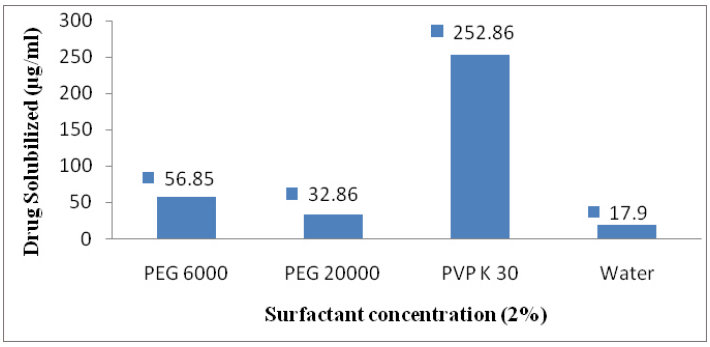

Figure 1: Extent of solubilisation of gliclazide in different surfactants solution

Dissolution studies of gliclazide

Three formulations were done with distilled water. The ratios of gliclazide with PEG 6000 were 1:11 / 1:20 / 1:40. Results showed that the cumulative drug release was <1% (table 2).

Table 2: Dissolution study results for different formulations (F1-F3) in distilled water

Formulation code	Drug: Polymer	Ratio	Dissolution media	% Highest cumulative drug release in 3 hrs	Comments
F1	Gliclazide:PEG6000	1:11	Distilled water	0.88	Insignificant change
F2	Gliclazide:PEG6000	1:20	Distilled water	0.67	Insignificant change
F3	Gliclazide:PEG6000	1:40	Distilled water	0.52	Insignificant change

After that one formulation was done with PEG 20000 and the ratio was with gliclazide 1:11. It was assumed that the cumulative drug release would be increased, but it was only 0.24 % (table 3).

Table 3: Dissolution study results for formulation F4 in distilled water

Formulation code	Drug: Polymer	Ratio	Dissolution media	% Highest cumulative drug releasein 3 hrs	Comments
F4	Gliclazide:PEG20000	1:11	Distilled water	0.24	Insignificant change

As distilled water did not give good results, then dissolution media was changed and it was Phosphate buffer solution @ pH 7.4. Here the ratio of gliclazide and PEG 6000 were 1:6 / 1:10. The cumulative drug release was double and it was highest for 1:6, but for 1:10 it was remain same as before. A ratio of 1:3:3 of gliclazide, PEG 6000 and PEG 20000 was also taken to see the cumulative drug release in Phosphate buffer solution @ pH 7.4. The cumulative drug release was third highest (table 4).

Table 4: Dissolution study results for different formulations (F5-F7) in Phosphate buffer solution @ pH 7.4

Formulation code	Drug:Polymer	Ratio	Dissolution media	% Highest Cumulative drug release in 3 hrs	Comments
F5	Gliclazide:PEG6000	1:6	Phosphate buffer solution @ pH 7.4	1.81	Significant change
F6	Gliclazide:PEG6000	1:10	Phosphate buffer solution @ pH 7.4	0.70	Insignificant change
F7	Gliclazide:PEG 6000:PEG20000	1:3:3	Phosphate Buffer solution @ pH 7.4	0.63	Insignificant change

At last the highest cumulative drug release was compared with gliclazide and lactose in the same ratio to see the cumulative drug release in phosphate buffer solution @ pH 7.4. The result was second highest (table 5).

Table 5: Dissolution study results for formulation F8 in Phosphate buffer solution @ pH 7.4

Formulation code	Drug: Polymer	Ratio	Dissolution media	% Highest cumulative drug releasein 3 hrs	Comments
F8	Gliclazide:Lactose	1:6	Phosphate Buffer solution @ PH 7.4	1.44	Significant change

Physical parameters of gliclazide capsule

Physical parameters among the composition had been shown in following table (table 6) and figure (fig. 2) showed the weight uniformity of different formula (F1-F3 & F5).

Table 6: Physical parameter results for different formulations (F1-F8)

Formulation code	Drug : Polymer	Ratio	Angle of repose	Range of wt. uniformity (%)	Disintegration test	% of moisture permeation (After 7days)
F1	Gliclazide:PEG6000	1:11	30.600	96.4-104.1	Passed	1.49
F2	Gliclazide:PEG6000	1:20	28.160	96.92-104.7	Passed	0.78
F3	Gliclazide:PEG6000	1:40	28.840	95.93-103.38	Passed	1.52
F4	Gliclazide:PEG2000	1:11	ND	ND	ND	ND
F5	Gliclazide:PEG6000	1:6	29.540	97.3-102.98	Passed	1.36
F6	Gliclazide:PEG6000	1:10	ND	ND	ND	ND
F7	Gliclazide:PEG 6000 :PEG20000	1:3:3	ND	ND	ND	ND
F8	Gliclazide:Lactose	1:6	ND	ND	ND	ND

ND= Not done

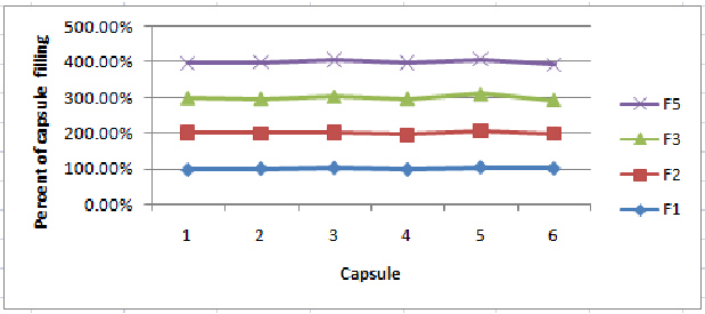

Figure 2: Weight uniformity test for different formulations (F1-F3 & F5)

Fourier transforms infrared (FTIR) spectroscopy

The IR spectra of SD (gliclazide and PEG 6000 in a ratio of 1:20), PM-water (Physical mixing by shaking with water) and PM-abs (Physical mixing by absolute alcohol) were compared with the standard spectrum of gliclazide (fig. 3). IR spectrum of gliclazide is characterized by the absorption of carbonyl (C=O) sulphonyl urea group at 1720 cm^{-1}. In spectra of SD, PM- water and PM-abs, this band was shifted towards lower frequencies at 1710, 1712 and 1704 cm^{-1} respectively. Also the NH group which is located at 3270 cm^{-1} from the IR spectrum of gliclazide shifted to 3278 cm^{-1} in SDs, 3272 cm-1 in PM-water and 3274 cm^{-1} in PM-abs. The sulphonyl group bands are located at 1356 and 1191 cm^{-1} in pure gliclazide. In SD, the asymmetric vibration peak of S=0 band was shifted from 1356 to 1341 cm^{-1} with decreased frequencies, in PM-water it was shifted to 1380 with increase frequencies and in PM- abs. it was shifted to 1354 cm^{-1}. In SD, the symmetric stretching vibration band of S=0 was shifted from 1191 to 1150 cm^{-1} with decreased frequencies in PM-water 1191 cm-1 and in PM-abs 1191 cm^{-1}. Important vibrations detected in the spectrum of PEG 6000 are the C–H stretching at 2925 cm^{-1}, C–O stretching at 1151 cm^{-1} and –OH stretching at 3455 cm^{-1}.

The shift in the peaks associated with sulfonylurea group of the gliclazide indicates an increase in bond strength possibly due to stabilizing effect of the hydrogen atoms of PEG 6000 interacting with the oxygen atoms of the sulphonyl group. Mentioned evidences thus lead to the conclusion that changes seen are as a result of physical interaction (hydrogen bonding or complexation) between the gliclazide and PEG 6000 in solid state. It could be expected to have hydrogen bonding between the hydrogen atom of the NH group of gliclazide and one of the ion pairs of oxygen atom in the PEG 6000.

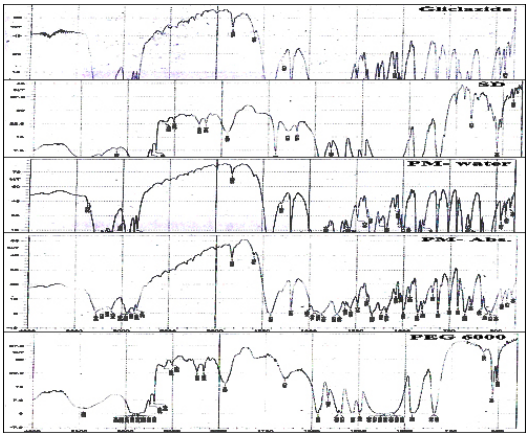

Figure 3: FTIR spectrograms of, (A): gliclazide; (B): Solid dispersion (SD= Gliclazide & PEG 6000 in a ratio of 1:20); (C) Physical mixture (PM- water= Physical mixing by shaking with water, PM- abs= Physical mixing by shaking with absolute alcohol); (D): PEG 6000

The objective of this study was to formulate and prepare glicazide capsule by solid dispersion, because there are a limited number of publications on solid dispersion in which formula was developed

by capsule. Moreover, capsules have some advantages over other dosage forms, such as- high dose accuracy, minimum excipients are required, tasteless, odorless, can be easily administered and attractive in appearance. Gliclazide is a BCS class II drug [13]. Low aqueous solubility and poor dissolution of this molecule, delays its rate of absorption and finally the onset of action. The rate and extent of absorption of BCS class II compound is highly dependent on the bioavailability which ultimately depends on solubility [14, 15]. In preliminary investigation on solubilisation study of gliclazide showed, solubility of PVP K 30 was more than the PEG 6000 and PEG 20000 with respect to water, but we preceded our work by polyethylene glycol. However, it is difficult to formulate the capsules by polyvinylpyrrolidone, as it is more hygroscopic. Thus, a greater understanding is required to formulate drug products successfully. Solid dispersion is one of the most promising approaches for solubility enhancement as it attracted considerable interest as an efficient means for improving the dissolution rate and hence the bioavailability of hydrophobic drugs. Fusion method was used successfully for the preparation of solid dispersion that offers a number of advantages. Our results showed that, capsules containing PEG 6000 had been given highest dissolution rate at 1:6 ratios. Capsules were also subjected to different physical parameter tests. IR spectra indicated no well-defined interaction between the drug and polymer.

Conclusion

The solubility and dissolution rate of gliclazide can be enhanced by formulating solid dispersion of gliclazide with PEG 6000. The solubilisation effect of PEG 6000 increased wettability, dispersibility and alteration of the surface property, which might be responsible for enhanced solubility and dissolution in a ratio of 1:6. Although, we formulated and prepared the gliclazide capsule by solid dispersion method but it had some lacings like- in vivo test, not compared with the marketed product. So, further study is required to improve this formula.

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