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Comparative Dissolution Study of Glipizide by Solid Dispersion Technique

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Abstract
The aim of this study was to increase the solubility and dissolution of Glipizide in water by solid dispersion. The solid dispersion of glipizide was prepared using water soluble carriers such as polyethylene glycol (PEG) and mannitol by fusion method and PVP K 30 by solvent evaporation method in an attempt to increase the solubility and dissolution rate of Glipizide- a practically insoluble drug in water. IR spectroscopy and in-vitro dissolution studies were used to characterize the solid dispersion. FTIR studies show no chemical interaction between Glipizide and PEG 6000, mannitol and PVP K 30. The solid dispersion prepared in this study was found to have higher dissolution rate and solubility compared to plain drug and physical mixture of drug and carriers. It was found that the optimum weight ratio 1.5 for PEG-6000 shows higher solubility and dissolution rate. Finally it was concluded that PEG-6000 shows greater dissolution enhancing capacity than mannitol and PVP K 30.

Introduction

Solid dispersion which was introduced in the early 1970s, in essentially a multi-component system, having drug dispersed in and around hydrophobic carriers.(1)

In order to improve the solubility and bioavailability of poorly water soluble drugs many methods are used. The solid dispersion approach has been widely used for improvement solubility, dissolution rate and hence bioavailability of poorly water soluble drug. (2)

In order to improve solubility and dissolution of poorly water-soluble drug many methods are used. Enhancing the bioavailability of poorly water-soluble drug carriers are of the most challenging aspect of drug development. (3) Among various approaches, solid dispersion has successfully improved dissolution rate of such drugs.

Solid dispersion technique has been used a variety of partially aqueous soluble drug such as nimusulide (4), ketoprofen (5), tenoxicam (6), nifedipine (7), nimodipine (8) . Various hydrophilic carriers such as PEG 6000 (9), PVP, HPMC, gums, sugars, mannitol, have been investigated foe improvement of dissolution characteristics and solubility of poorly water soluble drugs.

Glipizide is second generation sulphonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat non insulin dependent diabetes mellitus(10).It is oral hypoglycemic agent that is 100 times more potent than Tolbutamine, which is used for treatment of type II diabetes mellitus. As per BP it is practically insoluble in water (classification as BCS class II drug). Glipizide dosage form show poor solubility and dissolution and hence considered as rate determining step in its absorption from gastrointestinal tract. (11)

Material and Methods

Material

Glipizide was obtained as a gift sample from USV ltd Mumbai. PEG –6000 and mannitol was purchased from Merck India Ltd, Mumbai. All other chemicals used were of analytical regent grade. Freshly prepared distilled water used throughout the study.

Preparation physical mixture:-

Physical mixture (PM) of Glipizide with PEG-6000, mannitol and PVP K 30 in ratio 1:1, 1:2, 1:3, 1:4, 1:5 ratio was prepared by thoroughly mixing the accurately weighed quantity of drug and carrier in glass mortar and pestle for 5 min.and stored in a dessicator for 24 hours.

Preparation of Solid Dispersion by Fusion method [12]

Physical mixture was melt in a water bath with gradual increasing of temperature up to the

value necessary for the complete melting. The molten mass was rapidly cooled with constant stirring using a glass rod. The resulting solid dispersion were grounded in mortar for 2 min and passed through sieve no. 100. The prepared dispersions were stored desciccator in glass vials and used for further studies. The formulations were named P1, P2, P3, P4 and P5 prepared from PEG 6000 and M1, M2, M3, M4 and M5 that of Mannitol.

Preparation of solid dispersion by Solvent evaporation method. [13]

Accurately weighed quantity of carriers PVP K 30 in various 1:1, 1:2, 1:3, 1:4, 1:5 (drug: carrier) proportion were carefully transferred into glass flask and dissolved in dichloromethane. To these solutions, accurately weighed quantities of glipizide were added and allowed to dissolve. Then solvent was removed by evaporation at 40 ^{0} C under reduced pressure by using vacuum evaporator (Kumar, India.) The mass obtained in each flask was scraped, crushed, pulverized and sifted through mesh No. 100. Formulations were named as R1, R2, R3, R4 and R5.

1) Determination of Drug content [9]

The percent drug content of each solid dispersion, was determined using powder equivalent to 50 mg Glipizide and was dissolved in minimum amount of methanol and volume was made up to mark 100ml using pH 7.4 phosphates buffer. The solution was then filtered through Whatman filter paper no. 42 and required dilution were being made and assayed for drug content using UV double beam spectrophotometer at 276 nm. Three replicates were prepared and average value was reported.

2) Solubility Study [14]

Solubility study was assessed out according to the method of Higuchi and cannors. The solubility of Glipizide as pure drug and its solid dispersion were determined in distilled water and phosphate buffer pH 7.4. Glipizide and solid dispersion equivalent to 10mg of drug was taken and to this 10 ml of respective medium was being added in 100 ml stoppered volumetric flask and shaken foe 25 hrs at RT on magnetic stirrer. The entire samples were protected from light by wrapping the flask by aluminum foil. After 24 hr samples were filtered through Whatman filter paper no. 42 and aliquots were suitably diluted and assayed spectroscopically at 276 nm.

Each solubility was determined in triplicate and average values were reported.

3) In-vitro dissolution studies [13]

Dissolution study was carried out by using USP rotating basket (apparatus-I) (Electrolab) for 2 hr. the stirring rate was 100 rpm. Phosphate buffer pH 7.4 and distilled water was used as medium (900 ml) and was maintained at 37 +/- 5^0 C. samples equivalent to 5mg of Glipizide was filled in hard gelatin capsule used for dissolution studies. Samples were collected at regular interval of time and assayed for dissolution spectroscopically at 276 nm. Each dissolution rate test was repeated thrice and average values were reported.

4) FTIR studies: -

The FTIR spectra of the drug, PEG-6000, mannitol and solid dispersion in different ratio were recorded with FTIR spectrophotometer (Jasco V-6001). The samples were prepared by using potassium bromide and scanned for the absorbance at 4000-400/cm

Result and Discussion

Drug content:

The content of Glipizide in each preparation was assayed by UV spectroscopy. The assay values were between 97% to 99% of the theoretical value.

Phase Solubility studies:

Solubility profile of Glipizide with PEG 6000, mannitol and PVP K 30 are shown in table 1. The solubility of Glipizide in water and in phosphate buffer, without PEG 6000, PVP K 30 and mannitol was found to be 0.0365 mg ml^{-1}. The solubility of Glipizide increased as a

linear function of carrier concentration. All the solid dispersions shows enhanced solubility but higher in case of solid dispersion prepared by PEG 6000(1:5 ratio).

Table 1: Solubility of Glipizide from various solid dispersion in phosphate buffer pH 7.4

Solid dispersion	Solubility Distilled water (mg/1000ml)	Solubility (phosphate buffer) (mg/1000ml)
Plain Drug	36.5	55.86
P1	75.97	103.09
P2	91.47	119.23
P3	103.20	148.30
P4	121.74	172.61
P5	137.72	193.28
R1	64.13	76.61
R2	79.46	98.04
R3	91.78	108.62
R4	98.08	134.81
R5	110.90	145.95
M1	41.88	63.38
M2	52.66	79.85
M3	64.26	87.46
M4	70.18	92.24
M5	76.33	114.00

Dissolution Studies:

In vitro dissolution study was carried out for pure drug and all formulation in distilled water as well as in phosphate buffer pH **7**.4. The dissolution curve of Glipizide from various solid dispersions presented in figure1-3.The release rate profile were plotted as the percentage glipizide dissolved from the solid dispersion and pure Glipizide verses time. Figure 1-3 showed the dissolution profile of Glipizide with PEG 6000, PVP K 30 and mannitol at different drug carrier ratio.

In case of pure drug only 32.17% and 34.35% was dissolved at the end of 2 hours in distilled water and phosphate buffer pH 7.4 respectively, but the dissolution of the drug was increased with increase in the carrier ratio in the formulations. The order of drug dissolution from different carriers is PEG 6000>PVP K 30 >mannitol.

From the result obtained, it can be seen that in phosphate buffer pH7.4, Glipizide: PEG 6000 solid dispersion (1:5 ratio), the percent release was found 94.26% upto 2 hours (figure 1) and Glipizide: PVP K 30 solid dispersion (1:5 ratio), the percent release was found 86.07 % while Glipizide: mannitol solid dispersion (1:5 ratio) shows 82.73% drug release (figure3). This result demonstrates that gilpizide dissolution rate is significantly enhanced by solid dispersion method.

Table 2: Cumulative % drug dissolved from solid dispersion prepared using PEG 6000 in phosphate buffer pH 7.4

Time (min)	Batch code*				
	P 1	P 2	P 3	P 4	P 5
0	0	0	0	0	0
5	14.83	16.61	15.17	15.69	16.98
10	36.86	39.03	39.07	45.41	45.08
15	44.14	46.81	47.74	59.01	67.00
30	48.78	53.47	54.51	64.48	82.87
45	50.50	54.64	56.73	68.59	91.05
60	50.09	56.86	57.12	68.90	94.81
120	51.64	58.81	59.68	71.30	94.20

Table 3: Cumulative % drug dissolved from solid dispersion prepared using PVP in phosphate buffer pH 7.4

Time (min)	Batch code*				
	R1	R 2	R 3	R 4	R 5
0	0	0	0	0	0
5	03.81	15.75	15.87	17.21	17.32
10	04.90	20.25	32.71	37.40	38.90
15	08.17	36.08	39.80	43.09	45.19
30	18.92	44.11	56.08	76.00	75.92
45	21.14	48.73	63.83	81.21	82.07
60	31.92	49.90	71.00	83.07	84.71
120	35.96	51.98	74.91	83.70	86.07

Table 4: Cumulative % drug dissolved from solid dispersion prepared using Mannitol in phosphate buffer pH 7.4

Time (min)	Batch code*				
	M1	M 2	M 3	M 4	M 5
0	0	0	0	0	0
5	03.73	13.17	15.67	16.93	17.07
10	04.51	19.18	31.19	36.37	36.90
15	08.12	35.67	38.35	40.07	41.17
30	17.98	43.90	55.07	67.81	69.70
45	20.83	47.93	60.61	73.39	79.21
60	30.91	48.68	63.09	76.07	81.43
120	34.87	50.60	71.57	81.90	82.73

Figure 1: Cumulative % drug dissolved from solid dispersion prepared using PEG 6000 in phosphate buffer pH 7.4

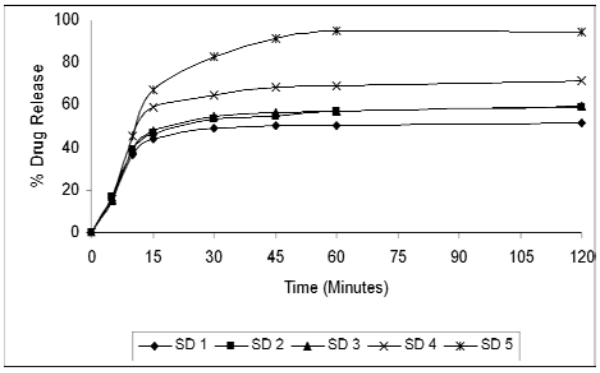


Figure 2: Cumulative % drug dissolved from solid dispersion prepared using PVP in phosphate buffer pH 7.4

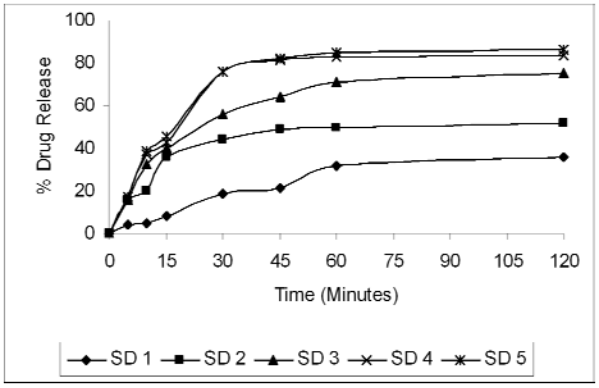
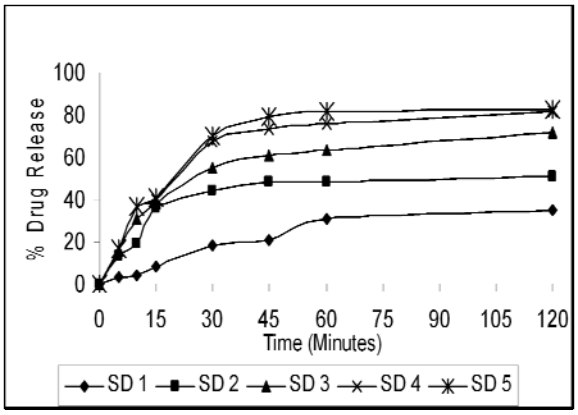


Figure 3: Cumulative % drug dissolved from solid dispersion prepared using Mannitol in phosphate buffer pH 7.4



FTIR study:

FTIR was performed on Glipizide, PEG 6000, PVP K 30 and mannitol solid dispersion of Glipizide with all carriers. The IR spectra of solid dispersion showed all the principal IR absorption peak of Glipizide 3324 cm-1, 3051 cm-1, 1648 cm-1, 1395 cm-1. FTIR of solid dispersion of drug and all carriers shows that all the peaks of drug and carrier as it is and drug is present in free form. This indicates that there is no interaction in between Glipizide and the entire carrier employed in solid dispersion.

Conclusion:

The increase in the solubility and dissolution rate of Glipizide is achieved either with PEG 6000 and mannitol solid dispersion prepared by fusion method and with PVP by solvent evaporation method. An increase in the proportion of carrier significantly improved solubility and dissolution rate. The result of dissolution study showed that Glipizide: PEG 6000 solid dispersion had faster dissolution rate than Glipizide itself. In contrast with carriers, it seems that interaction of solid dispersion had not occurred in Glipizide and carriers. Finally it was concluded that PEG 6000 shows greater solubility and dissolution enhancing capacity than mannitol

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