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Der Pharmacia Lettre, 2009, 1 (2) 255-261
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ISSN 0975-5071

Development, Optimization and *In-Vitro* Evaluation of Glibenclamide Solid Dispersion Using Different Polymer

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Abstract

Drugs administered orally in solid dosage form should dissolve in gastrointestinal fluids before they are absorbed. Drugs with united solubility in aqueous media may exhibit dissolution rate limited absorption profile. Thus the rate of dissolution of the drugs in the gastrointestinal fluids could influence the rate and extent of absorption. In the case of poorly soluble drug the dissolution rate always influences its absorption. These solid dispersions provided sustained absorption of nifedipine in beagle dogs with good availability after oral administration. Stability studies indicated that these dispersions were stable for at least 6 months under accelerated conditions. Similar dispersions of dipyridamole also showed delayed absorption with good bioavailability.

Keywords: eutectic mixture, inert carrier, microcrystalline, molecular dispersion,

Introduction

Chiou and Riegelman, 1971 defined the term solid dispersion as “A dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method.” Drugs administered orally in solid dosage form should dissolve in gastrointestinal fluids before they are absorbed. Drugs with united solubility in aqueous media may exhibit dissolution rate limited absorption profile. Thus the rate of dissolution of the drugs in the gastrointestinal fluids could influence the rate and extent of absorption. The different ways of increasing the rate of absorption or total bioavailability of drugs. In 1961, a new approach of solid-dispersion was devised and demonstrated by Sekiguchi and Obi. This provided a new approach to particle size reduction and increased rates of dissolution. Sekiguchi and Obi proposed the formation of a eutectic mixture of a poorly soluble drug such as Sulphathiazole with a physiologically inert, easily soluble carrier such as Urea. The

method involves the preparation of a microcrystalline or molecular dispersion of the drug in a solid-matrix of water-soluble physiologically inert carrier like urea. The melted sulphathiazole and urea was followed by rapid solidification. The fine dispersion of the drug in the solid eutectic mixture and the rapid dissolution of the soluble matrix promoted a fast release of the drug into the surrounding fluid. [1, 2, and 3]

Material and methods

Glibenclamide Supplied by Maan pharmaceutical Ltd. Absolute Alcohol S.D. Fine Chem. Ltd., Mumbai. Sodium hydroxide, Polyethylene Glycol 6000, Polyvinyl Pyrrolidone K30, Potassium bromide (KBr), Methanol, and absolute alcohol from S.D. Fine Chem. Ltd., Mumbai, Qualigen Chemicals, and India supplied Hydrochloric acid. Potassium dihydrogen ortho phosphate by Ranbaxy Fine Chemicals Limited, India.

UV Spectrophotometer Systronics 2201 UV/Vwasible double beam Spectrophotometer (Japan). Dwassolution test apparatus Dwassolution test apparatus-TDT-06T (Electrolab, Mumbai, India). pH meter Systronics, 361-micro pH meter. IR Spectrophotometer Shimadzu 8400 S FTIR Spectrophotometer (Japan). DSC DSC- Shimadzu 60 was used.

Solid dispersions prepared by melting of the carrier: Four solid dispersions (SDs) preparations containing different weight ratios of GLB in PEG 6000 (1:1, 1:5, 1:10, and denoted as MEPEG 1/1, 1/5, 1/10, respectively) were prepared by the melting method (Frances, et al., 1991). GLB was added to the melted PEG 6000 at 75°C and the resulting homogeneous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24 h. Subsequently, the dispersion was ground in a mortar and sieved through 50 #.

Solid dispersions prepared by Co-evaporation: SDs of GLB in PEG 6000 or PVP K30 containing different weight ratios (1:1, 1:5, 1:10, and denoted as CEPEG or CEPVP 1/1, 1/5, 1/10, respectively) were prepared by the co-evaporation method as follows (Christian & Jennifer, 2000). To a solution of GLB (5 mg) in ethanol (25 ml) the appropriate amount of PEG 6000 or PVP K30 was added. Next, the solvent was evaporated under reduced pressure at 40°C and the resulting residue, dried under vacuum for 3 h, was stored in a desicator for at least overnight, ground in a mortar, and passed through a 50 # sieve.

Physical mixture: Physical mixtures (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of GLB and PEG 6000 or PVP K30 in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a 50 # sieve and denoted as PMPVP or PMPEG, respectively [5, 6, 7, 9, 10, 11 and 13].

Characterization of solid dispersions of GLB with PEG 6000 & PVP K30, [15, 17, 18]

Differential Scanning Calorimetry (DSC) Analysis: DSC curves obtained for pure GLB, PEG, PVP, their PMs and SDs prepared with PEG and PVP are shown in Fig and. Pure powdered GLB showed a melting endotherm at 225°C with enthalpy of fusion (ΔH) 302.22 ml/g. DSC scan of PEG showed single sharp endotherm at 58°C due to melting of PEG whereas during scanning of PVP, a broad endotherm ranging from 80 to 120°C was observed, due to the presence of residual moisture in PVP. DSC thermo grams of PMPEG 1/10 and PMPVP 1/10 showed the melting peak

of the drug at 225°C and sharp endothermic peak at 58°C due to melting of PEG and the broad endotherm due to the presence of water ranging from 80 to 120°C in PVP. [16]

Fourier transform IR spectroscopy: FTIR spectra were recorded using KBr pellet method in the region of 400-2000 cm^{-1} . Background spectrum was collected under identical conditions. The spectrum for each sample can average of 16 co-added scans was recorded at a resolution of 4cm^{-1} , Fourier transformed and ratio against background interferogram. Spectra were recorded for pure drug and pure excipients.

Dissolution Study: Dissolution studies of all samples were performed using USP XXIII apparatus type 2 for 4 hour. Samples of pure GLB, PMs and SDs equivalent to 20 mg of the drug were added to the dissolution medium (900 ml of phosphate buffer pH 7.2 at a temperature of $37^\circ\text{C} \pm 0.3^\circ\text{C}$), which was stirred with a rotating paddle at 80 rpm. At suitable time intervals, 10 ml samples were withdrawn, filtered, diluted and analyzed at 228 nm using UV spectrophotometer. Equal volume of fresh medium pre-warmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate and calculated mean values of cumulative drug release were used while plotting the release curves. MDT values & f_2 values were calculated for comparison of release of GLB from diff samples.[4, 12]

Study of release rate kinetics [9]: Different kinetic models (zero-order, first-order, Higuchi's equation and Korsmeyer's equation) were applied to interpret the drug release kinetics from matrix system with the help of Equations 1-4.

$$M_t = M_0 + k_0 t \quad \dots \dots \dots (1)$$

$$\ln M_t = \ln M_0 + k_1 t \quad \dots \dots \dots (2)$$

$$M_t = M_0 + k_H t^{1/2} \quad \dots \dots \dots (3)$$

$$M_t/M_\infty = k_k t^n \quad \dots \dots \dots (4)$$

In these equations, M_t is the cumulative amount of drug released at any specified time point and M_0 is the dose of the drug incorporated in the delivery system. k_0 , k_1 , k_H and k_k are rate constants for zero order, first order, Higuchi and Korsmeyer's model respectively. For the same number of parameters, the coefficient of correlation (R²) can be used to determine the best of the model equations.

Stability protocol: Accelerated stability studies have been carried out on final formulation batch of the product containing different composition. Solid dispersion storage conditions and sampling plan for stability studies. Accelerated ($40^\circ\text{C} \pm 2^\circ\text{C}/75\% \pm 5\% \text{RH}$) room temperature ($30^\circ\text{C} \pm 2^\circ\text{C}/60\% \text{RH} \pm 5\%$) for 15, 30 and 90days.

Results and Discussion

DSC (Differential Scanning Calorimetry): showed the melting peak of the drug at 225°C and sharp endothermic peak at 58°C due to melting of PEG and the broad endotherm due to the

presence of water ranging from 80 to 120°C in PVP. **Fig 1, 2** show that there is no interaction between polymer and drug.

IR spectra: The compatibility evaluations were performed by FTIR spectroscopy analysis. The study implies that the drug and polymers are compatible with each other. There were no interaction found between polymers and drug.

Dissolution Studies: on comparative dissolution studies were carried out by keep in phosphate buffer (pH 7.2) at interval of 4hour for solid dispersion of different ratio(i. e. 1:1, 1: 5, 1:10) and three different methods and results were satisfactory for solid dispersion by co evaporation methods(CE 1:10) found to be 97.55%) in **graph:**

Release rate kinetics:

High values of correlation coefficient (R²: 0.9150- 0.9915) were obtained when fitted to Higuchi equation compared to first order, zero order and Korsmeyer equations. From these results, the Higuchi model seems the best-fitted model, which indicates a dissolution-controlled release.

Stability Studies of Optimized formulation: Stability Studies of Optimized formulation

From the results shown in graphs, it can be inferred that the physical appearance of the tablets, remained unchanged at the end of 15, 30 & 90th day for (CE 1:10) at room temperature and at 40°C±2°C/75±5% RH FOR 90days. Results show no change in physical appearance and *invitro* dissolution. Hence solid dispersion was found stable at tested temperature (**graphs 7, 8**).

Characterization of solid dispersions of GLB with PEG 6000 and PVP K 30

Calibration curve for glibenclamide in phosphate buffer pH 7.2

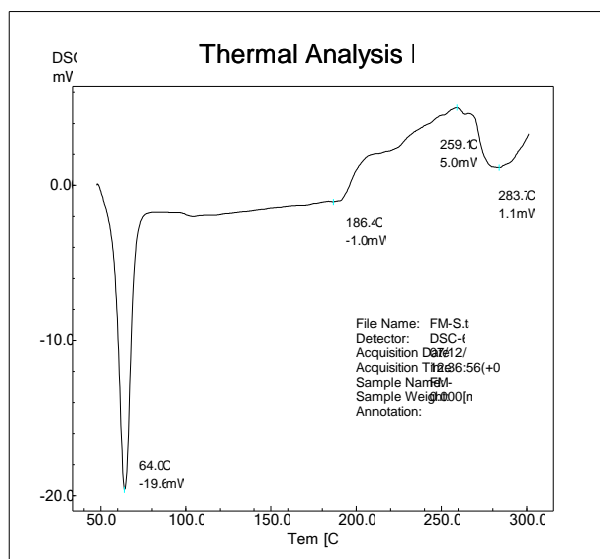


Figure No 1. FM-S (1:10) With PEG 6000

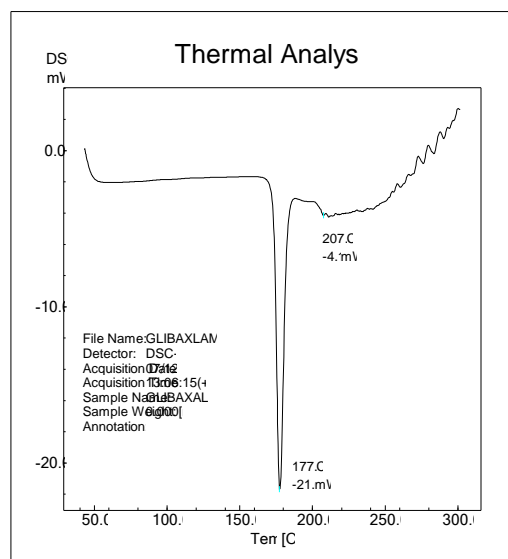
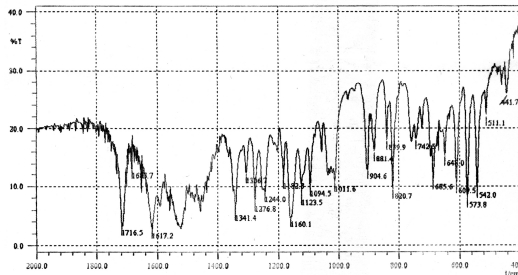


Figure No 2. Glibenclamide

Compatibility study by FTIR
Compatibility study with pure drug and best formulation

By comparing the peaks I can be said that there is no incompatibility.

FTIR STUDIES



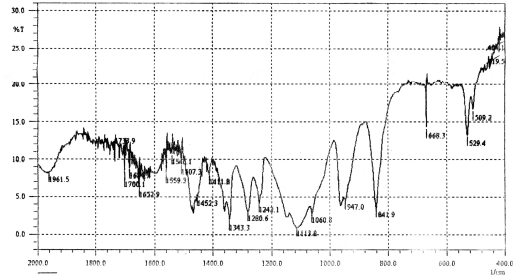
Peaktable of G128304.DS (1), 24 Peaks

Operator: NETA Origin: Sujat Laboratory
 Date: 02/05/07 15:54:12

Threshold: 50, Noise: 5, Min range selection

No.	Pos. (1/cm)	Inten. (1/T)
1	441.67	25.84
2	541.90	22.48
3	541.98	9.74
4	722.78	8.07
5	805.04	10.10
6	880.04	15.04
7	885.45	11.16
8	1022.54	10.31
9	1025.55	9.09
10	1025.54	10.10
11	1091.41	16.11
12	1094.25	13.09
13	1091.39	10.09
14	1094.23	10.08
15	1137.44	10.43
16	1160.10	4.74
17	1162.08	11.10
18	1244.10	5.05
19	1276.09	7.04
20	1276.08	12.10
21	1341.60	7.04
22	1637.20	2.77
23	1689.74	13.13
24	1716.33	2.77

Glibenclamide
 G-304



Peaktable of PEG305.DS (1), 22 Peaks

Operator: NETA Origin: Sujat Laboratory
 Date: 02/05/07 15:54:12

Threshold: 50, Noise: 5, Min range selection

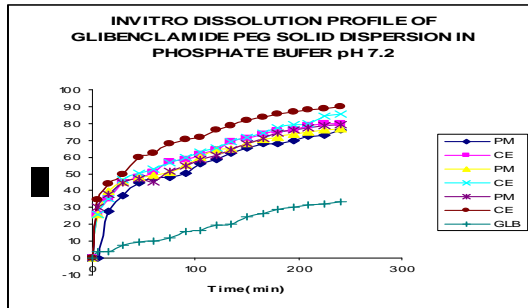
No.	Pos. (1/cm)	Inten. (1/T)
1	404.96	21.57
2	420.49	24.43
3	500.17	10.76
4	575.42	17.27
5	689.25	10.75
6	841.87	3.54
7	946.90	4.42
8	1001.70	3.40
9	1171.91	0.99
10	1247.07	4.23
11	1320.65	1.09
12	1341.37	2.50
13	1411.90	7.50
14	1467.70	5.54
15	1577.27	9.14
16	1540.05	10.71
17	1550.14	0.70
18	1618.80	4.74
19	1669.70	0.89
20	1700.11	0.55
21	2187.80	0.43
22	3041.47	0.24

PEG 6000
 G-305

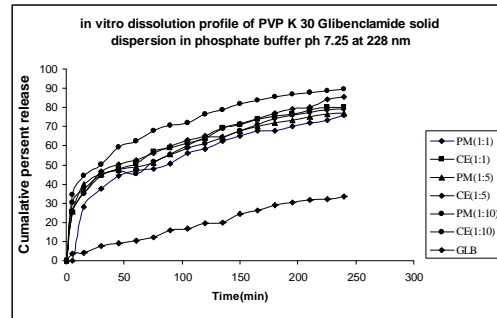
Figure No. 4 IR Spectrum of Glibenclamide

Figure No. 5 IR Spectrum of PEG-6000

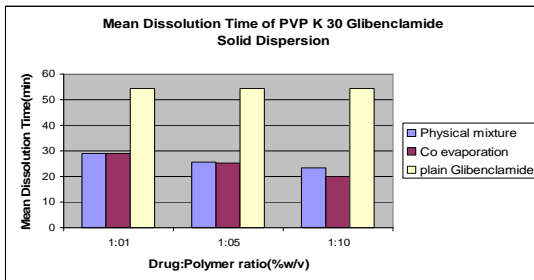
Graphs:



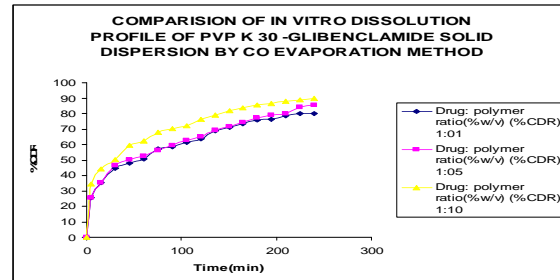
Graph: 1



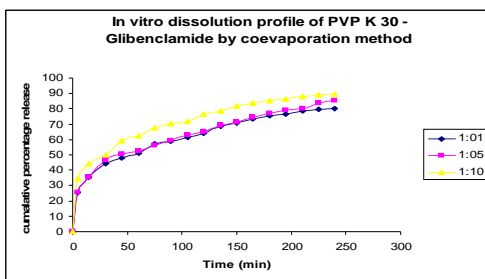
Graph: 2



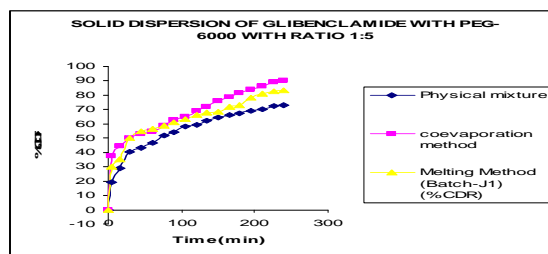
Graph: 3



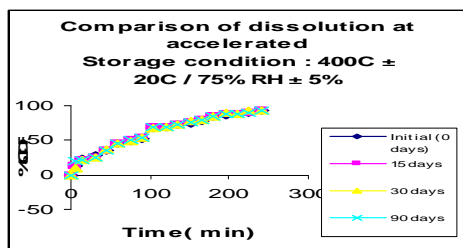
Graph: 4



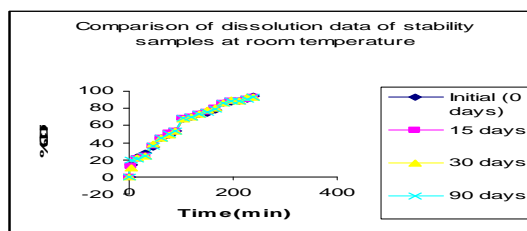
Graph: 5



Graph: 6



Graph: 7



Graph: 8

Conclusion

The solid dispersions of GLB with PEG & PVP have been prepared in different weight ratios by using methods like melting, co-evaporation and physical mixing. Phase solubility studies showed a significant solubilizing effect of both polymers on GLB at different temperatures. The Gibbs free energy and enthalpy of transfer indicated spontaneous nature of GLB solubilization in aqueous solution of both polymers. FTIR, DSC. In this system, trapping of drug inside polymeric matrix was demonstrated using FTIR. The highest improvements in solubility and *in-vitro* drug release were observed in solid dispersion prepared with PEG by co-evaporation method. The solubility & *in-vitro* drug release from the physical mixture, when compared to that of the solid dispersion, was improved to a lesser degree. The dissolution rates of physical mixtures were higher than that of pure drug.

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