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Enhancement of Solubility of Gliclazide by Solid Dispersion

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Abstract : The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Once if we are able to increase the aqueous solubility of a drug, the disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved. Solid dispersions must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. The initial solubility of pure drug Gliclazide was found to be 8µg/ml. Solid dispersion of Gliclazide was prepared using Polyethylene glycol 4000,Polyethylene glycol 6000,Mannitol,Low substituted Hydroxy propyl cellulose as carriers by Kneading, solvent evaporation and Solusorb method respectively. Different ratios 1:1, 1:3, 1:9 of drug: carrier is taken. The maximum enhancement of solubility was found in Kneading method of ratio 1:1 using drug: low substituted hydroxy propyl cellulose with 250%.
Keywords: Gliclazide, Polyethylene glycol 4000, Polyethylene glycol 6000, Mannitol, Low substituted hydroxy propyl cellulose.

Introduction and Experimental

Chiou and Riegelman (1971) defined solid dispersion as "a dispersion of one or more active ingredients in an inert carriers or matrix at solid state prepared by the melting (fusion), solvent evaporation or melting-solvent method[1,2]". The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Bioavailability can be defined as the rate and extent at which the drug is delivered to the systemic circulation from dosage form and reaches the site of action to produce the desired effect. Solid dispersions must be developed into convenient dosage forms, such as capsules and tablets, for their clinical use and successful commercialization. Formulation of fast release regimen of soluble or insoluble drugs is enhanced by using soluble or insoluble carriers. Solid dispersion of drugs in solid state is helpful in stabilizing unstable drugs.

The PEGs may protect certain drugs ex: cardiac glycosides against the decomposition by saliva and allow buccal absorption. Solid dispersions may be a thermodynamically more active form of drug and directly influence the diffusion and release rate. The oral administration of solid dispersions without concomitant reduction in dose may result in higher incidence of adverse effects. The increased dissolution rates from solid dispersions were attributed to the reduction of particle size of the drug within the dispersions and increased wettability.

Preliminary Investigation on Solubility of Gliclazide [3]

25ml of the medium [distilled water] was taken in three stoppered conical flasks and an excess quantity of Gliclazide was added to these stoppered conical

flasks and shaken for 24 hrs by using mechanical shakers. At the end of 24 hrs period, the solution was filtered through Whatman No. 41 filter paper and the filtrate was suitably diluted with 0.1N NaOH and the drug content was estimated Spectrophotometrically at λ_{max} of 227 as shown in **Table - 1.**

Table 1: Solubility of Gliclazide at room temperature. (n = 3)

Solvent	Solubility in µg/ml
Distilled water	8

Effect of Carriers on the Solubility of Gliclazide

0.5, 1, 2, 3% solutions of polymers (LHPC, Mannitol) were prepared with 25 ml of distilled water in stoppered conical flasks, to this each conical flask an excess quantity (100 mg) of drug was added and shaken for 24 hrs by using mechanical shakes. After 24 hrs, the solutions were filtered through Whatman No. 41 filter paper and the filtrates were suitable diluted with 0.1N NaOH and the drug contents were estimated spectrophotometrically. The results thus obtained were summarized in the **Table-2.**

Table 2: Effect of carriers on the solubility of GLZ

Concentration (%)	LHPC	Mannitol
0.5	**10**	**3**
1	**10**	**40**
2	**17**	**45**
3	**9**	**41**

From the above study it was concluded that all the carriers have an effect on the solubility of Gliclazide in water. All the carriers used caused an increase in the solubility of the drug in water.

Preparation of Solid Dispersions [4, 5]

Preparation of Physical Mixtures:

Accurately weighed quantities of drug and carrier were taken in a glass mortar and were mixed thoroughly. The resultant mixture was passed through sieve number 100 and was stored in a desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: polymer ratios of 1:1, 1:3 and 1:9 were prepared.

Solvent Evaporation Method:

Drug and carrier were weighed according to the required drug: carrier rations of 1:1, 1:2, 1:3 and 1:9 to the drug methanol was added to get a clear solution, to third appropriate amount of carrier was added. To the above a minimum amount of methanol was again added to solubilize the polymer. The solvent was allowed to evaporate by continuous trituration. Then the mass was further dried in desiccators for 2 days. The dried product was crushed, pulverized and sieved through 100 mesh. The solid dispersions thus obtained were stored in a well-closed container and kept in desiccators.

Kneading Method:

Drug and carrier in different ratios were triturated in a mortar with a small volume of methanol: water (1:5) solvent blend. The thick slurry was kneaded for 45 mins, and then the mass was further dried in desiccators for 2 days. The dried product was crushed, pulverized and sieved through 100 mesh. The solid dispersions thus obtained were stored in a well-closed container and kept in desiccators.

Solusorb Method:

Gliclazide was added into the melt of surfactant, maintaining a temperature slightly higher than the melting point of surfactant to obtain a clear molten mixture. Magnesium Aluminium Silicate (MAS) was preheated to 80°C in the beaker containing magnetic stirrer for 15 mins. The molten mixture was then added drop-wise over a period of one min to MAS with continued stirring. Hot-melt granulation was performed at an increased stirring speed for one more minute to obtain the ternary dispersion granules of drug, PEG-6000, PEG-4000 & Magnesium Aluminium Silicate. The dispersion granules are allowed to come to room temperature by air cooling followed by sieving through mesh # 18.

Evaluation of Solid Dispersion Systems [6,7]

The prepared solid dispersions were evaluated for their:

- Drug Content
- Solubility studies
- Infra Red spectral analysis
- Differential Scanning Calorimetry

Drug Content Estimation:

The GLZ solid dispersions, which were prepared and tested for drug content. From each batch of solid dispersions (prepared in different ration) equivalent to 10 mg of DMP were taken and analyzed by proposed method for drug content. The drug content for all the prepared formulations was found to be within the range i.e. 95 – 100% w/w

Solubility Studies of Various Solid Dispersion Systems

25ml of the medium [distilled water] was taken in stoppered conical flasks and a quantity equivalent to 10 mg of Gliclazide solid dispersion was added to these stoppered conical flasks and shaken for 24 hrs by using mechanical shakers. At the end of 24 hrs period, the solutions were filtered through Whatman No. 41 filter paper and the filtrate were suitably diluted with 0.1 N NaOH and the solubility studies with different methods and polymers were estimated as shown in Table 3 , 4 and 5 . A bar diagram comparison was done for all the methods as shown in Figure 1, 2 and 3. One Way ANOVA was applied to determine the significant difference in % increase in solubility among the different methods in comparison to pure drug as shown in Table 6 and 7.

Table 3: Solubility Studies with LHPC

Drug :LHPC	Method	Solubility (µg/ml)	% increase
1:1	**Physical mixing (PM)**	14.5	181.25
1:3	**PM**	15	187.5
1:9	**PM**	16	200
1:1	**Solvent evaporation (SE)**	18	225
1:3	**SE**	14	175
1:9	**SE**	15	187.5
1:1	**Kneading(KN)**	20	250
1:3	**KN**	15	187.5
1:9	**KN**	**Not formed**	**Not formed**

Table 4: Solubility Studies with Mannitol

Drug :Mannitol	Method	Solubility (µg/ml)	% increase
1:1	**Physical mixing (PM)**	15.5	193.75
1:3	**PM**	14	175
1:9	**PM**	14	175
1:1	**Solvent evaporation(SE)**	5	62.5
1:3	**SE**	8	100
1:9	**SE**	8	100
1:1	**Kneading (KN)**	14	175
1:3	**KN**	6	75
1:9	**KN**	5	62.5

Table 5: Solubility Studies with Mannitol PEG4000 and PEG6000

Drug:PEG4000	Method	Solubility µg/ml	%increase
1:1	**Solusorb**	7	87.5
1:3	**Solusorb**	10	125
1:9	**Solusorb**	14	175
Drug:PEG6000			
1:1	**Solusorb**	7	87.5
1:3	**Solusorb**	8	100
1:9	**Solusorb**	12	150

Table 6 ONE – WAY ANOVA

Pure drug (%increase in solubility)	Physical mixing (%increase in solubility)	Kneading (%increase in solubility)	Solvent evaporation (%increase in solubility)
8	200	250	225
8.1	199	236	226
7.9	201	264	224

Table 7 ONE – WAY ANOVA

Source of Variation	Degree of Freedom	Sum of Squares	Mean Square	F Calculated Value	F Table Value
Treatment (Between columns)	3	109700	36570	738.7	
Residual (Within columns)	8	396.0	49.50		

Calculated F value is greater than F table value. So null hypothesis is rejected. Therefore it is concluded that there is extremely significant difference in % increase in solubility among the different methods in comparison to pure drug.

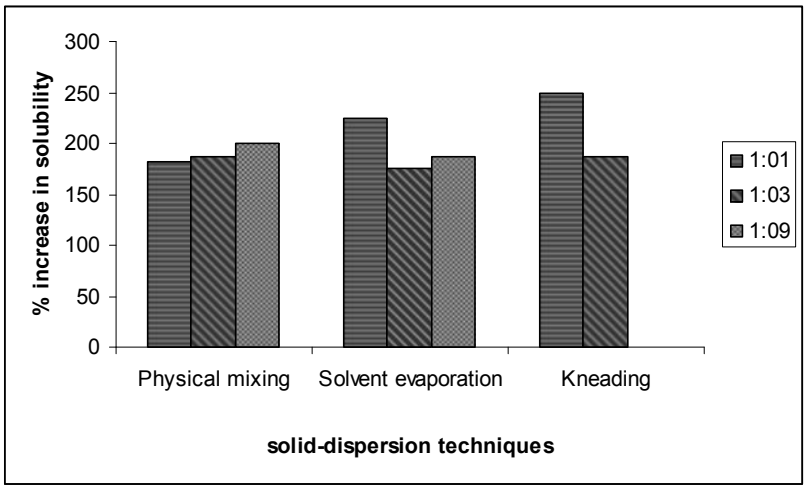

Figure 1: Comparison of % increase in solubility in case of L-HPC

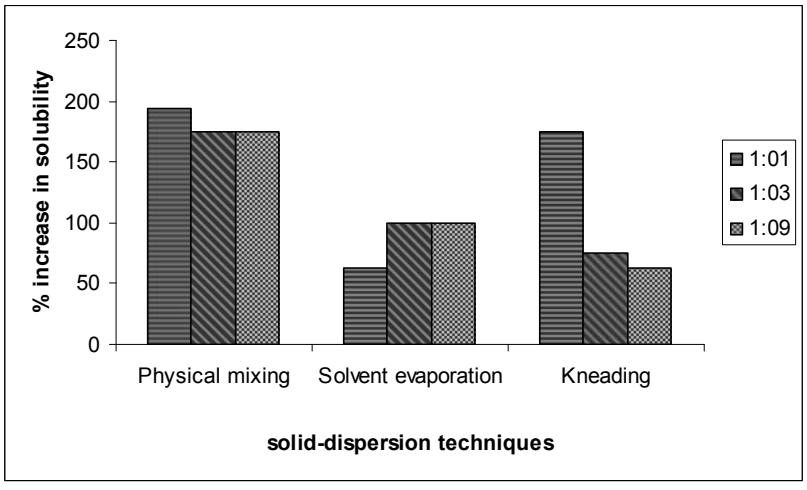

Figure 2: Comparison of % increase in solubility in case of Mannitol

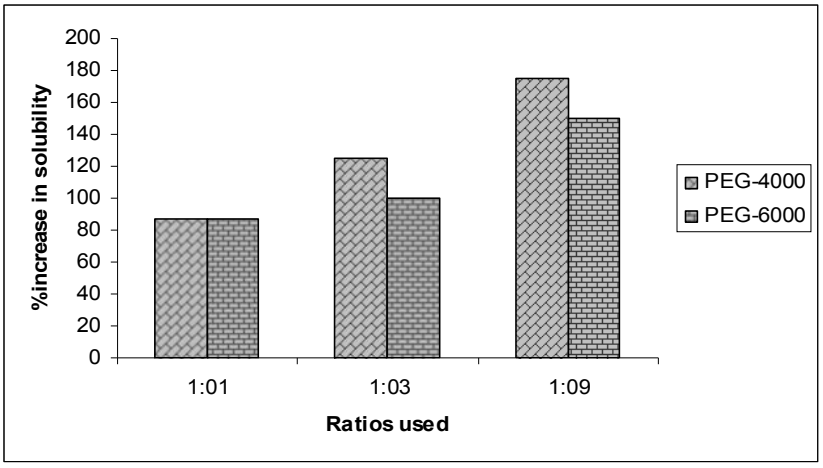

Figure 3: Comparison of % increase in solubility in case of both PEG-4000 and PEG-6000

DSC Studies

DSC patterns of samples were obtained with Shimadzu DSC – 50 instrument using vented aluminium pans. For DSC analysis each sample of 5-10 mg weight was taken in hermetically sealed flat – bottomed aluminium pans. The sample was heated over a temperature range of 30 - 300°C in nitrogen atmosphere (30ml/min) at constant rate of 10°C/min. the instrument was calibrated with standard medium. DSC graphs are shown in Figure 4, 5 and 6.

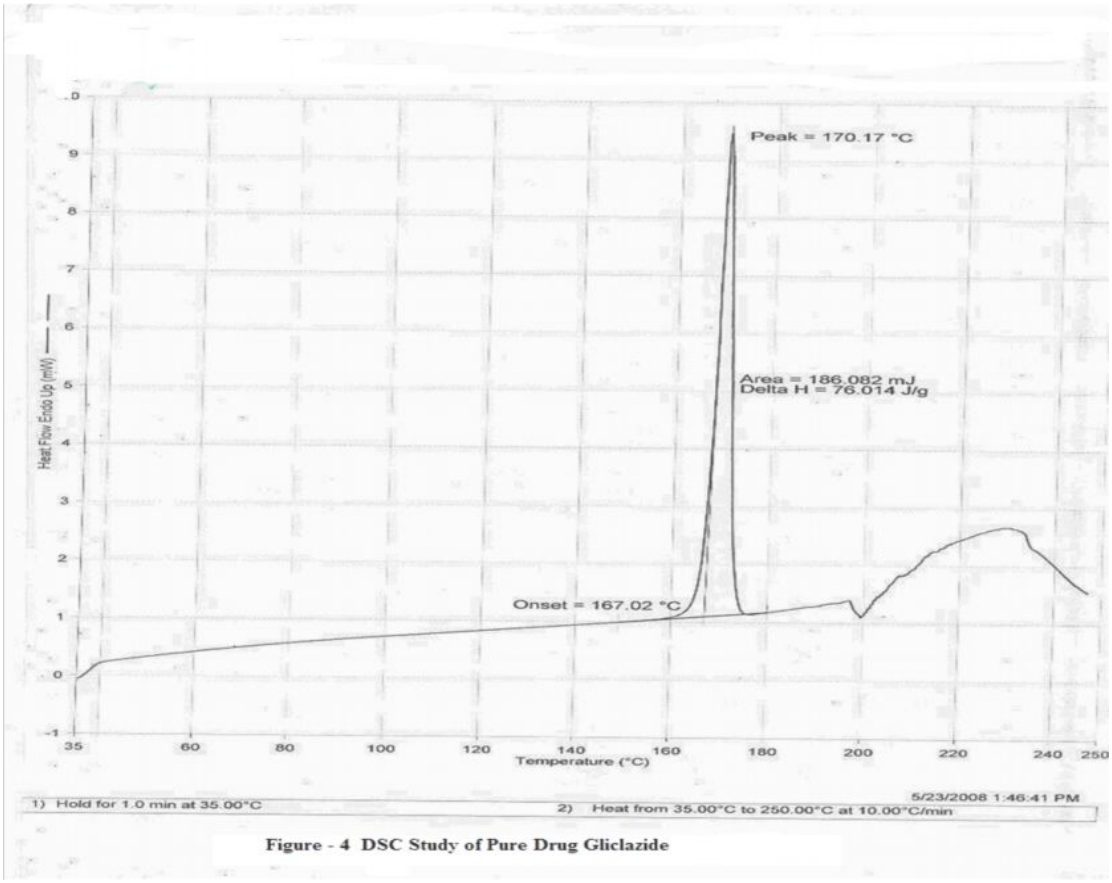

Figure 4: DSC thermogram of pure Gliclazide

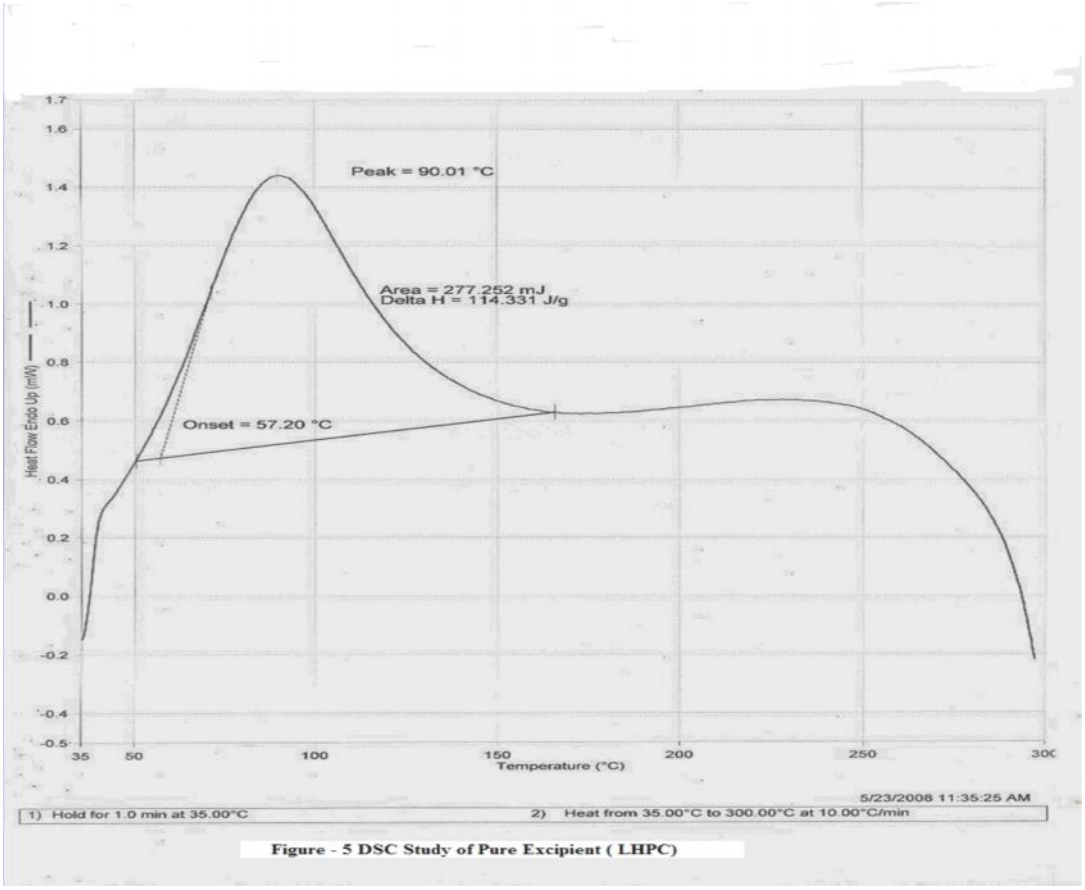

Figure 5: DSC thermogram of pure LHPC

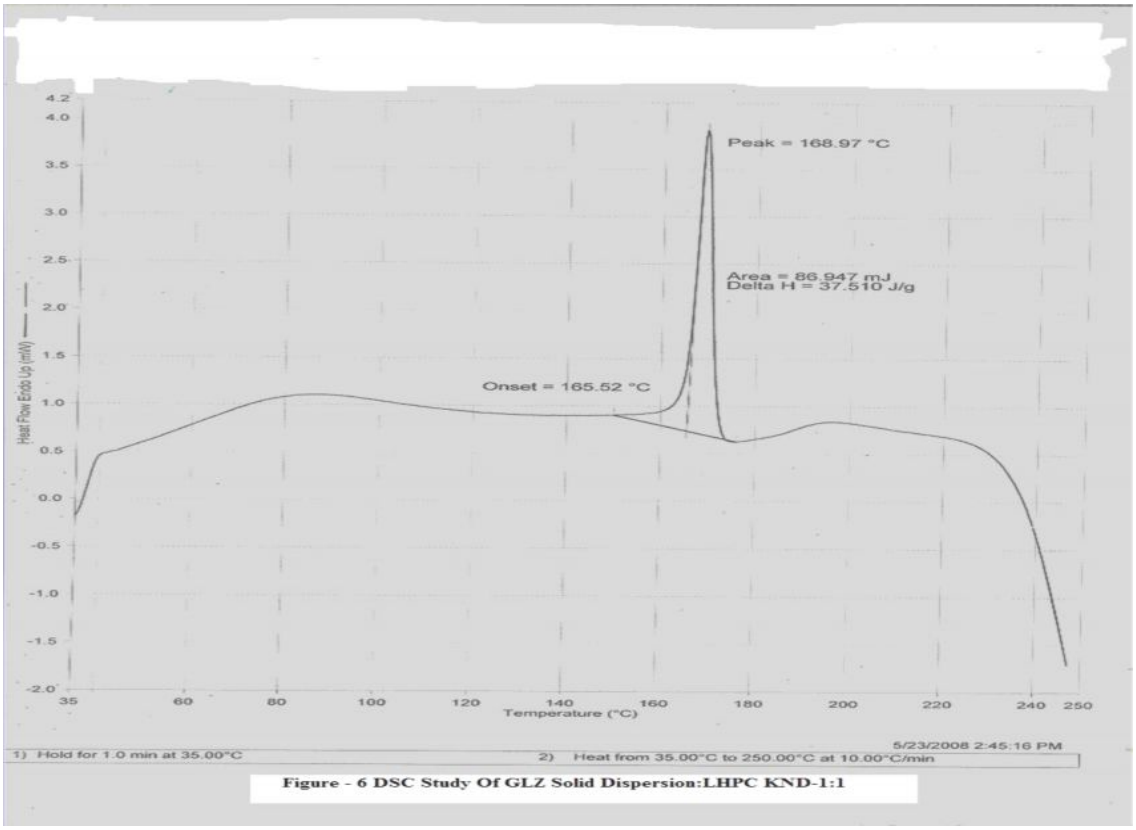

Figure 6: DSC thermogram of Gliclazide Solid dispersion: LHPC KND 1:1

Results and Discussion

Studies were undertaken on the preparation and evaluation of solid dispersion of Gliclazide with a view to develop fast release formulation of Gliclazide. In these studies, the possibility of improving the solubility and dissolution rate of Gliclazide via solid-dispersion with L-HPC, Mannitol, PEG-4000, and PEG-6000 were explored and their physical properties were studied. The effect of L-HPC, Mannitol, PEG-4000, and PEG-6000 on the solubility was studied for pure drug, physical mixture and solid-dispersion. Solid-dispersions were prepared by using solid-dispersion techniques like solvent-evaporation, Kneading, Physical mixing, Solusorb methods. The solid dispersions prepared were found to be white in color, fine and free flowing powders.

Solubility studies of pure drug and solid-dispersion were performed in distilled water. The drug solubility in distilled water was found to be 8 µg/ml as shown in Table – 1. The Gliclazide solid-dispersions were tested for drug content and was found within the compendia limits (95 – 100 %). Gliclazide didn't show any degradation during preparation of solid dispersion as checked by determining the drug content in the solid dispersions, which were within the limits of 95 – 1000% w/w, and by measuring the λ_{max} in 0.1N NaOH which didn't show any shift (227 nm). All the solid dispersions prepared were found to be uniform in drug content. The effect of carriers on solubility of Gliclazide is shown in Table – 2.

The solid-dispersion was prepared in 1:1, 1:3, 1:9 ratios. In case of solvent-evaporation maximum increase in solubility was found to be 200 in 1:1 ratio with L-HPC and 100 in 1:3 ratio with Mannitol as polymer, Whereas for kneading method maximum increase was found to be 250 in 1:1 ratio with L-HPC and 175 in 1:1 ratio with Mannitol as polymer, In case of physical mixing 200 was the % increase in solubility in 1:9 ratio with L-HPC and 193.75 in 1:1 ratio with Mannitol as polymer. But in Solusorb method maximum increase was 175 and 150 in 1:9 ratios with PEG-4000 and PEG-6000 as shown in table- 4.c. The % increase in solubility is represented in bar diagram as shown in Figs- 3, 4 and 5 respectively.

All the carriers used for the preparation of solid dispersions showed significant increase in the solubility of Gliclazide.

LHPC > Mannitol > PEG 6000 > PEG 4000

In comparison of all the techniques of solid-dispersion maximum enhancement was found to be in Kneading method in 1:1 ratio (250%).

All the maximum values of % increase in solubility were exposed to one – way ANOVA in comparison to pure drug. Calculated F value is greater than F table value. So null hypothesis is rejected. Therefore it is concluded that there is extremely significant difference in % increase in solubility among the different methods.

DSC thermo grams of Gliclazide, L-HPC, and L-HPC: Gliclazide (1:1 kneading) are shown in DSC graphs respectively. The DSC thermo grams of pure Gliclazide shows an endothermic peak at 170.17°C , pure L-HPC shows a peak at 90.01°C and Gliclazide solid dispersions shows a sharp peak at 168.97°C .Since the drug melting peak is retained there is no interaction between drug and the excipients.

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