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COMPARATIVE DISSOLUTION RATE STUDIES OF PIOGLITAZONE HCL LIQUID SOLID COMPACTS AND SOLID DISPERSION TABLETS

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ABSTRACT

The absorption rate of poorly water-soluble drug, from the orally administered solid dosage form is controlled by its dissolution rate in the fluid present at the absorption site. The dissolution rate of poorly soluble, highly permeable (BCS_II) drugs, such as Pioglitazone HCl, can be improved by the application of the solid dispersions (SD) and liquisolid (LD) technique. In this study, the different formulations of liquisolid compacts using different co-solvents (non-volatile solvents like propylene glycol (PG) and PEG400) and solid dispersion with PEG4000/ PEG6000 were prepared and the effect of several amounts of them on the dissolution behaviour of Pioglitazone HCl was investigated. Liquisolid compacts of Pioglitazone HCl were prepared by using Avicel PH 101, Aerosil 200 and SSG as carrier material, coating material and disintegrant, respectively. Liquisolid compacts and solid dispersion tablets were prepared and evaluated for characteristics like hardness, disintegration time and dissolution rates. To evaluate any interaction between Pioglitazone HCl and the other components in liquisolid formulations and solid dispersions, FTIR, XRPD and DSC analysis were used. The results showed that the liquisolid formulations exhibited significantly higher drug dissolution rates in comparison with directly compressed and solid dispersion tablets. The enhanced rate of Pioglitazone HCl dissolution derived from liquisolid tablets was probably due to an increase in wetting properties and surface area of drug particles available for dissolution. In conclusion, the results of this work suggest that liquisolid technique is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drugs.

INTRODUCTION:

For formulating a drug in a suitable dosage to provide maximum therapeutic effect with minimum dosage interval is primary concern for any dosage form. In that scenario, solubility and dissolution properties of drugs play an important. Most of the available drugs are of varying solubility ranges for which different techniques has to be incorporated to improve proper absorption of drug in body. This is an important physicochemical property of drug, especially aqueous solubility. The drug must be presented in solution form for absorption through gastrointestinal tract (GIT). In the case of poorly soluble drugs, dissolution is the rate-limiting step in absorption process. Thus the bio-

availability of poorly water soluble drug is often limited to its dissolution rate. Various techniques are reported to improve the dissolution of poorly soluble drugs, including micronization, cyclodextrin complexation, use of surfactants and solubilizers[1], solid dispersion in water soluble and dispersible carriers, use of salts, pro drugs and polymorphs which exhibit high solubility, micro emulsions and self emulsifying micro and nano disperse systems [2], and the use of mesoporous silica carriers[3]. Recently, the liquisolid technique[4] has shown promise for improved dissolution. Solid dispersions (SDs) traditionally have been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs.[5] Solid dispersion the dispersion of one or more active ingredients in an inert hydrophilic carrier or matrix at solid state prepared by the fusion, solvent or solvent–fusion method. Solid dispersions prepared by kneading and physical mixture method are widely and successfully applied to improve the solubility and consequently the bioavailability of poorly soluble drugs.[6] Reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. The concept of liquisolid tablets was developed from powdered solution technology that can be used to formulate liquid medication.[7] A liquisolid system is defined as dry, non-adherent, free-flowing and compressible powder mixtures converted from liquid drugs, drug suspensions or drug solutions in nonvolatile solvents with selected carriers and coating materials.[8] In this technique, the drug is dissolved in a non-volatile liquid and converted to dry, free flowing and compressible solid using carrier and coat materials.[4] Since non-volatile solvents are used to prepare the drug solution/suspension, the liquid is not evaporated and the drug is carried in a liquid system and is dispersed throughout the final product. A mathematical model by Spireas and Bolton[4] was used to calculate the required quantities of carrier and coating material to be added to produce acceptable flow and compressibility. Pioglitazone, a widely prescribed oral antidiabetic drug belongs to class II under BCS and exhibit low and variable oral bioavailability due to its poor aqueous solubility. The oral absorption of pioglitazone is dissolution rate limited and it requires enhancement in the solubility and dissolution rate for increasing its oral bioavailability.

In the present study, among the various techniques for enhancing solubility, solid dispersion and liquisolid compacts are been used for piloglitazone by using hydrophilic polymers. Comparative studies of prepared different methods of piloglitazone tablets were investigated. Inorder to identify the most suitable methodology to elicit its renounced therapeutic effect with minimum dosage interval.

MATERIALS AND METHODS

Materials: Pioglitazone was a gift sample obtained from Dr. Reddy's Laboratories.PG, PEG 6000, PEG4000, were purchased from yarrow chemicals, Mumbai. All other chemicals used were of analytical grade.

METHODOLOGY

Saturation solubility studies: To select suitable solvent for preparation of liquisolid compacts solubility studies of Pioglitazone HCl were carried out in different solvents like distilled water, propylene glycol and PEG400. Saturated solutions prepared in vehicles were kept in an orbital shaker for 72hrs at 25˚C. The solutions were filtered and their concentration was determined by using Elico SL 159 UV-spectrophotometer at 269nm. The results were extrapolated to determine the percent w/v of Pioglitazone HCl in its saturated solution with the solvent under investigation.

Preparation of conventional tablets

Pioglitazone HCl conventional tablets were produced by mixing the drug (15mg) with avicel- aerosil mixture (ratio of Avicel/aerosil was 10:1). The mixture was mixed with sodium starch glycolate (SSG) (as disintegrating agent) for 10min, and compressed on a tablet compression machine. Sufficient compression load was applied in order to produce tablets with acceptable hardness. The formulation was denoted as DC total weight of tablet 200mg.

Preparation of liquisolid compacts

Various liquisolid compacts containing 15mg Pioglitazone HCl were prepared by dispersing in nonvolatile vehicles such as propylene glycol and PEG400. Then a binary mixture of carrier (Avicel ph 101) and coating material (Aerosil-200) was prepared at a ratio of 10:1. This binary mixture was added to the admixture of drug and vehicle. For the reported Φ-value the liquid load factor (*L*f) was calculated. Depending upon the type of vehicle in the formulation, different load factors were employed in liquisolid preparations.[9] Different concentrations of Avicel and Aerosil were used to prepare different liquisolid formulations. Finally SSG as a disintegrant was added to the above powder blend and mixed. The final powered blend was subjected to compression. The important formulation characteristics of liquisolid compacts are showed in Table 1.

Preparation of solid dispersion by solvent evaporation method

The solid dispersions were prepared using Pioglitazone HCl as drug and PEG4000/PEG6000 as carriers in the ratio of 1:1, 1:2, 1:3 as mentioned in Table 2. The required quantity of carrier (PEG4000/PEG6000) was weighed in electronic digital balance, taken in a mortar and it was dissolved completely in methanol by using pestle. Accurately weighed quantity of drug was then added to polymer solution. The solvent was then allowed to be evaporated at 40˚C over water bath. The solid dispersions were obtained after complete evaporation of the solvent. The solid dispersions were passed through sieve no 80 and stored in desiccators for further study. Tablets of solid dispersions were prepared using Avicel PH101, SSG, magnesium stearate and talc.

Characterization of liquisolid powders and solid dispersions

The compression parameters (angle of repose, Carr's compressibility index, Hausner's ratio) and post compression parameters (Weight variation, friability, hardness, disintegration test, drug content) were evaluated

In-vitro **dissolution studies:** The *in-vitro* release profiles of Pioglitazone HCl from directly compressed tablet, liquisolid compacts and solid dispersion tablets were obtained a dissolution test apparatus USP-II (electro lab). The dissolution study was carried out in 900ml 0.1N HCl as the dissolution medium at 37˚C±5˚C and 50rpm. Then 5ml samples were collected for 5, 10, 20, 30,45,60,90,120 mins. The dissolution medium was replaced with 5ml fresh dissolution fluid to maintain sink conditions. The withdrawn samples were filtered and analyzed, spectrophotometrically (Elico, SL 159) at 269nm. The mean of two determinations was used to calculate the drug release from each off the formulations.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra were obtained using a Bruker Alpha System with Spectrum opus 6.5software. A KBr pellet of drug, carrier, adsorbent and the solid dispersion granules were prepared. The sample was dispersed in the KBr and ground using a motor and

pestle. The KBr pellet was prepared by the application of high pressure.

X-Ray powder diffraction (XRPD)

XRPD was performed to observe the physical state of the solid dispersion and to evaluate any interaction between the drug, carrier and adsorbent in the solid dispersion. Philips PAN analytical X-Pert Pro V1.6 with X-Pert Data collector V2.1 software was used equipped with a cukα2 anode tube and diffractometer of radius 240mm. The XRD scan was performed using BB004 flat stage. The powered was placed in a plastic sample holder of 1 inch square. Data were collected at 45kv and 40ma. Samples were scanned from 0-40˚ 2θ at a step size of 0.0084 and scan rate of 1.00˚/min.

Differential Scanning Calorimetry: DSC studies were performed using a DSC (Siio-6300, Japan instruments). It is operated using stare software V8.10. A 3-5mg of sample was weighed and placed into a 100µl aluminium pan which is further crimped with a lid. The pan was then placed into the DSC unit along with a similar pan as a reference. The sample was scanned at a heating rate of 100C/min from 0˚C to 300˚C and purged under nitrogen gas flow rate of 50ml/min. The DCS was calibrated using indium (5-10mg) with a melting onset of 156±0.2˚C as the standard.

Stability Studies:

Stability studies were conducted for the optimized formulation. The FDA and ICH specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The study was performed under stability conditions at 40ºC ± 2ºC/75% RH ± 5% RH for three months.

RESULTS AND DISCUSSION

Solubility Studies: The solubility of Pioglitazone HCl in distilled water, propylene glycol and polyethylene glycol 400 was found to be 0.000743, 104.16 and 20.13mg/ml respectively as in Table 3. The solubility increases in the order as distilled water <PEG400< PG. Drug solubility is very poor in water, more solubility in PEG400 and greater solubility in PG. Pioglitazone HCl solubility is high in PG compared to others. Thus, among the solvents PG could be a better choice of solvent.

Pre compression parameters: The flow properties of the liquisolid granules and solid dispersions and its tablet powders are vital for the performance of the tablet. Hence the flow properties were analyzed before compression of the tablets. The compressibility index (≤22.56), Hausner's ratio (≤1.25) and the angle of repose (≤34.38) values indicated a good flow ability of granules.

Evaluation of liquisolid compacts and solid dispersion tablets

As the granules were free flowing, tablets produced were uniform weight with acceptable weight variation (≤1) due to uniform filling in the die. Hardness (3.0-4.0kg/cm^2) friability values (0.06-0.46) indicated that tablets had a good mechanical strength as shown in Table 4. All the formulations have disintegration time less than 1min. LS1 formulation exhibited least disintegration time of 36secs and DC exhibited highest disintegration time of 59sec.

Post compression parameters: All the parameters such as weight variation, friability, hardness, disintegration and drug content were found to be within limits as shown in Table 5. The average hardness for all the formulations was found to be from 3 to 4 Kg/cm^2 which were found to be acceptable. The average percentage friability for all the formulations was between 0.06 and 0.42, which was found

to be within the limit.Among liquisolid compacts LS1 (98.89%) showing maximum drug content and in solid dispersions TSD1 (88.8%) showing maximum drug content and TSD6 (77.2%) showing minimum drug content as in Table 5. Among all the formulations LS1 showed maximum drug content

In-vitro dissolution profiles

The drug release from conventional Pioglitazone HCl tablet was very poor. Only 44.94% and 53.59% drug was released in dissolution media in 60 and 90 min respectively as indicated in Figure 1 & 2. The effect of various dissolution enhancing agent (PG, PEG400 and PEG6000) on the drug release was studied by using Pioglitazone HCl. Among the liquisolid compacts containing drug and PG (10%w/w) exhibited greater drug release. The drug release was 68.34% and 101.72 in 10min and 20min respectively. Among the liquisolid compacts containing drug and PEG4000 (10%w/w) exhibited greater drug release. The drug release was 63.66% and 90.71 in 10min and 20min respectively. As the concentration of the solvent increased the % drug release and dissolution rate was also increased. And among the liquisolid compacts prepared with PG exhibited greater drug release rate and dissolution rate. Among the solid dispersion tablets, tablets containing drug and PEG4000 (1:1) exhibited greater dissolution rate. The drug release was 31.48% and 48.84% in 10min and 20 min respectively. Among the solid dispersion tablets, tablets containing drug and PEG4000 (1:1) exhibited greater dissolution rate. The drug release was 28.58% and 41.89% in 10min and 20 min respectively. As the concentration of the polymer increased drug release was decreased. Among the solid dispersion tablets, tablets with PEG4000 exhibited greater dissolution rate. Among the liquisolid compacts and solid dispersion tablets, liquisolid compacts with PG exhibited greater dissolution rate. LS1 exhibited greater dissolution rate among all the formulations. From all the dissolution profiles and dissolution rate release of the drug, LS1 was selected as the optimized formulation.

Compatibility studies

Fourier transform infrared spectroscopy (FTIR)

In the IR spectrum of Pioglitazone HCl, the pure drug formed a number of peaks prominently in different wave numbers indicating the presence of functional groups and substituent. A peak at 1037.18cm^{-1} indicates the presence of C-O medium stretching. A peak at 1742.7318cm^{-1} indicates the presence of C-O strong stretching. A peak at 1510.0718cm^{-1} indicates the presence of N-H medium bending. A peak at 738.68cm^{-1} indicates the presence of C-Cl strong stretching as shown in Figure 3. All the characteristic peaks were observed in the IR spectrum of drug- polymer physical mixtures. Hence, there was no interaction between the pure drug Pioglitazone HCl and other excipients. This, indicating drug and excipients are compatible. Polymorphic changes in the drug are important since they might affect the dissolution rate and inline bioavailability. So, it was necessary to study the polymorphic changes of Pioglitazone HCl in liquisolid systems and solid dispersion shown in Figure 4.. Pioglitazone HCl has sharp diffraction peaks at 20.23, 20.50, 21.19, 21.35, 23.28 at˚20. Solid dispersions with PEG4000 have a sharp diffraction at 19.81 at˚10 and solid dispersions with PEG6000 sharp diffraction peak at 23.96 at˚30. It has been observed that the diffraction peaks of solid dispersions are somewhat diffused compared to the diffraction patterns of Pioglitazone HCl. it also indicate the crystallinity of the solid dispersions are less than that of Pioglitazone HCl.

Table 1: Formulation table of Pioglitazone HCl liquisolid compacts

Liquisolid system	Liquid Vehicle	Drug concentration In liquid Medication(%w/w)	Excipient Ratio (R)	SSG (%)	Liquisolid Compact Weight (mg)
LS1	PG	10	10	10	676
LS2	PG	20	10	10	389
LS3	PG	30	10	10	239
LS4	PG	40	10	10	184
LS5	PG	50	10	10	155
LS6	PEG400	10	10	10	778
LS7	PEG400	20	10	10	409
LS8	PEG400	30	10	10	280
LS9	PEG400	40	10	10	225
LS10	PEG400	50	10	10	196

Table 2: Formulation table of Pioglitazone HCl solid dispersions

Solid dispersion		Drug: Carrier ratio	% yield
PEG4000	SD1	1:1	93.33
	SD2	1:2	91.66
	SD3	1:3	95.83
PEG 6000	SD4	1:1	90.22
	SD5	1:2	37.66
	SD6	1:3	91.66

Table 3: Solubility of Pioglitazone HCl in different solvents

Solvent	Solubility(mg/ml)
Distilled water	0.000743
PG	104.16
PEG 400	20.13

Table 4: Pre compression parameters of prepared pioglitazone liquisolid powders and solid dispersions

Formulation Code	Angle of Repose(θ)	Carr's compressibility index	Hausner's ratio
LS1	27.7	21.42	1.17
LS2	26.6	21.42	1.19
LS3	30.46	24.56	1.14
LS4	29.05	176	1.21
LS5	32	25	1.23
DC	30.96	18.36	1.23
SD1	26.9	7.92	1.08
SD2	25.7	16.32	1.04
SD3	28.88	16.99	1.17
SD4	27.5	17.02	1.20
SD5	28.8	18.36	1.22
SD6	27.45	15.62	1.18

Table 5: Post compression parameters of prepared pioglitazone liquisolid and solid dispersions Tablets

Formulation Code	Weight Variation (mg)	Friability (%)	Disintegration Time (sec)	Hardness (Kg/cm^2)	Drug Content (%)
LS1	675.7±0.15	0.14	36	4	98.89±1.4
LS2	388.9±0.51	0.24	40	3	97.23±1.7
LS3	238.4±0.4	0.32	43	3	96.12±2.2
LS4	184.2±0.25	0.42	45	4	97.26±1.9
LS5	157.6±0.65	0.32	43	4	98.12±2.3
DC	119.9±1.54	0.11	59	4	90.95±1.2
TSD1	205.8±0.25	0.09	50	3	88.8±1.9
TSD2	208.6±0.15	0.06	48	3	85.6±1.4
TSD3	198.4±0.19	0.17	54	3	78.8±2.9
TSD4	195.7±0.23	0.12	52	3.5	86.2±1.9
TSD5	205.1±0.5	0.09	43	3	83.3±2.1
TSD6	201.3±0.3	0.18	46	3	77.2±1.6

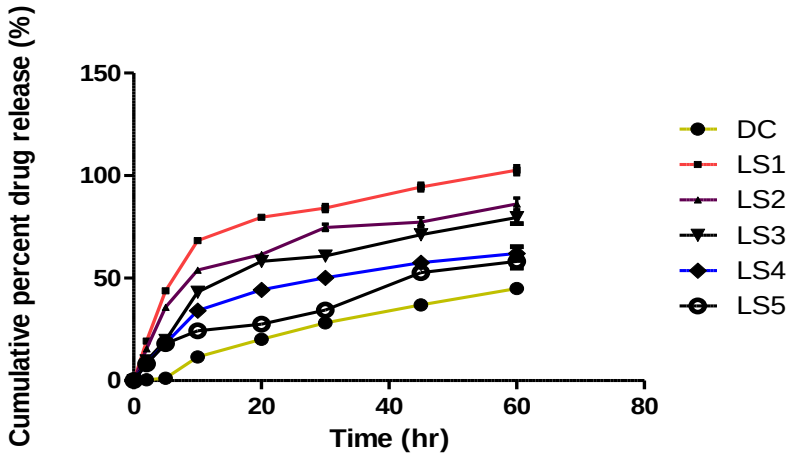
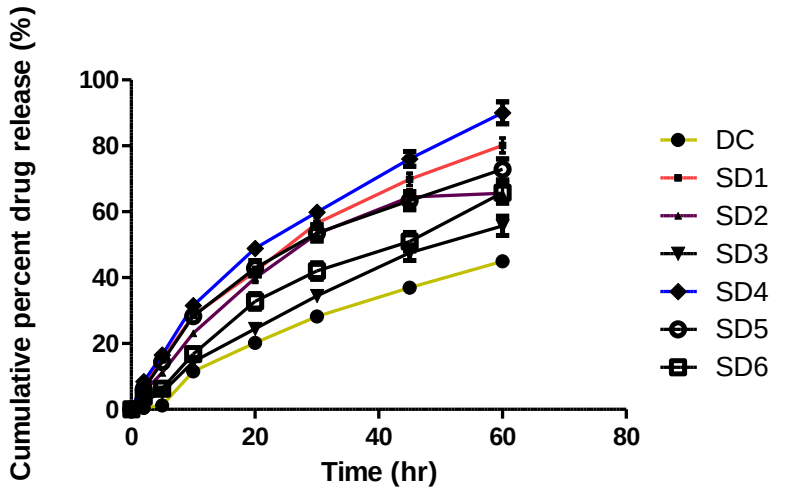


Figure 1: Drug release profiles of prepared Liquisolid tablets



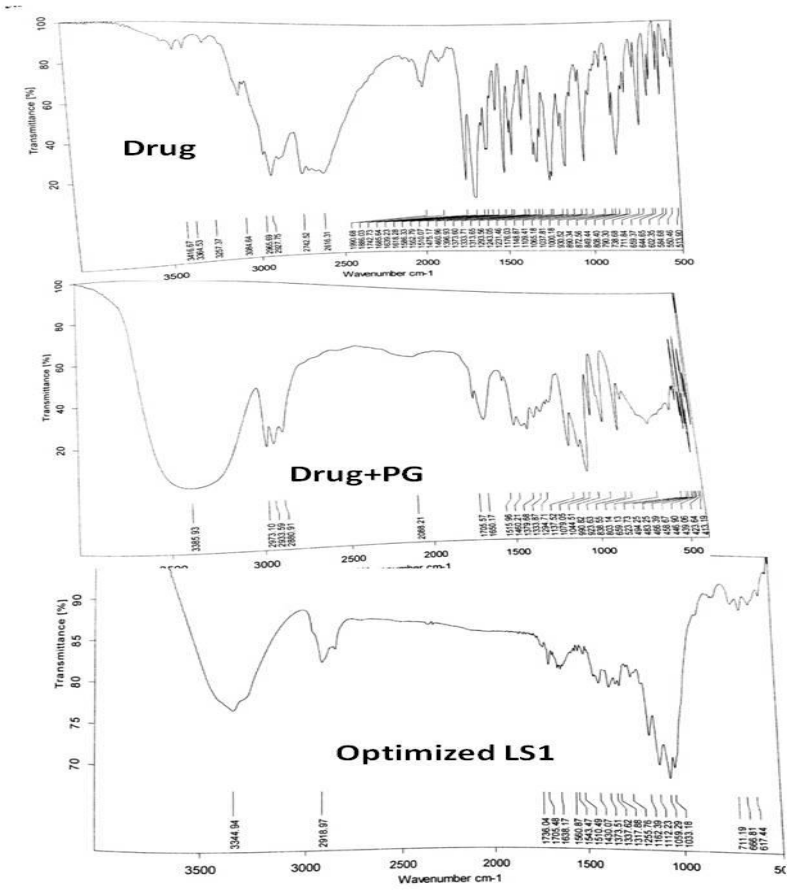


Figure 3: FTIR Spectras of drug and optimized formulation

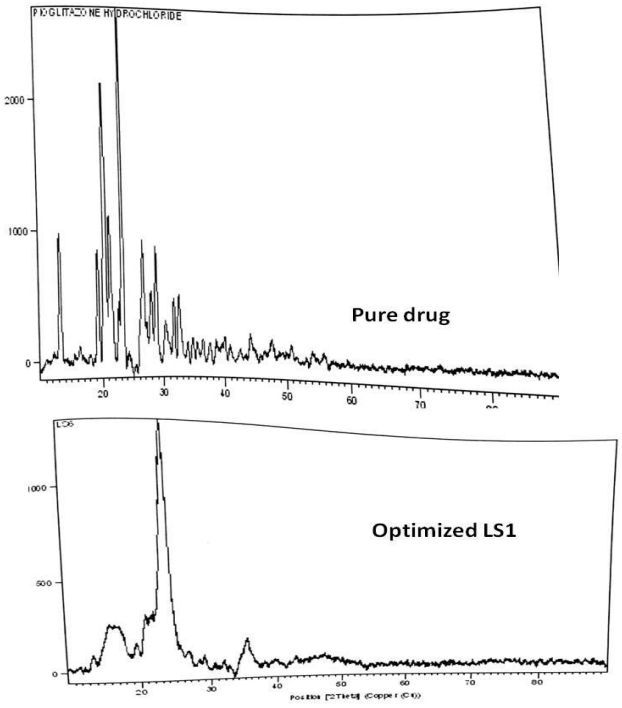


Figure 4: X-RD spectra's of drug and optimized formulation

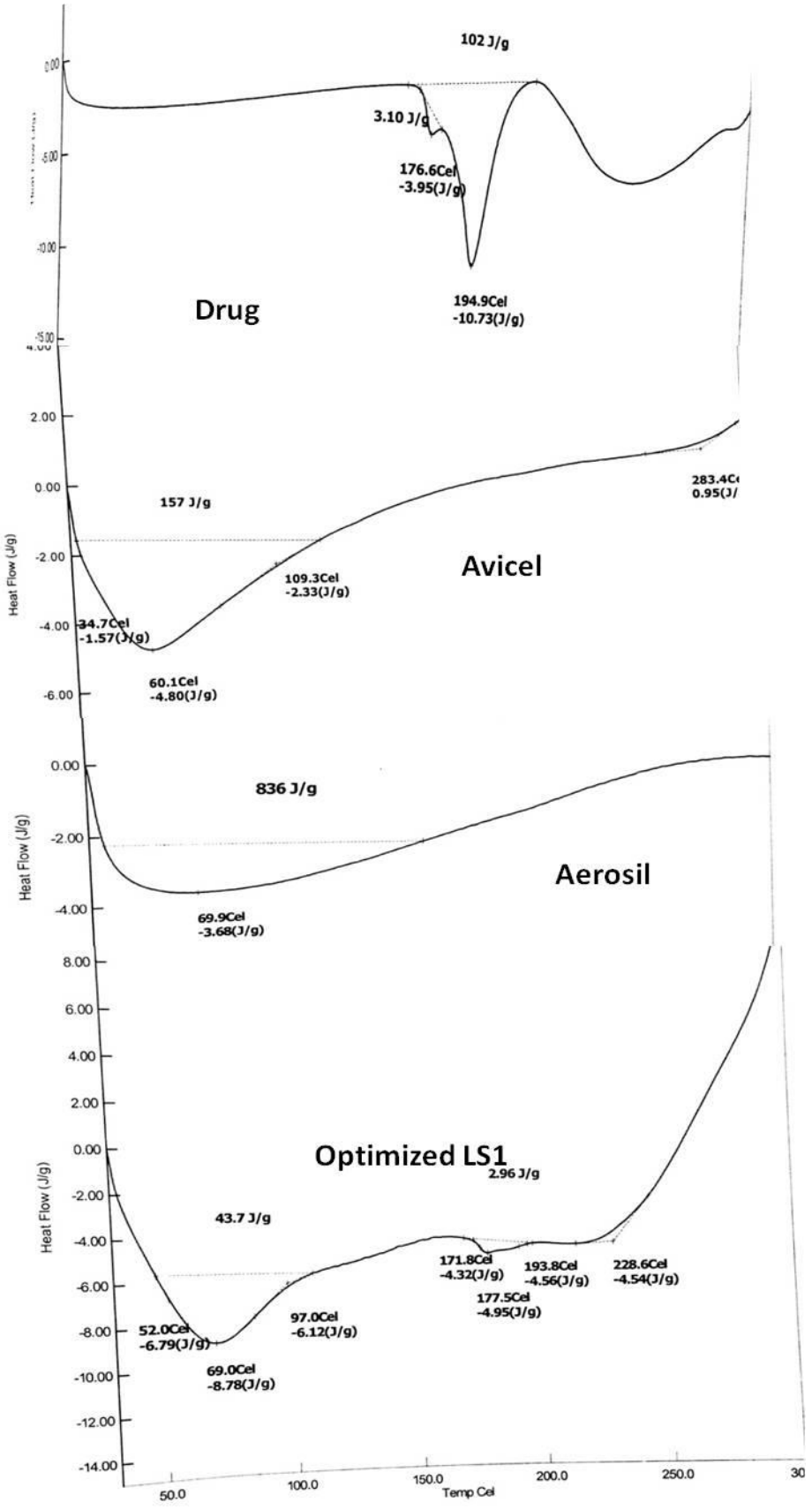


Figure 5: DSC thermographs of drug and optimized formulation

Avicel PH101 has sharp diffraction peak at 23.1 at˚30 while the liquisolid powder with PG had a sharp diffraction peak at 23.31 at˚20 and liquisolid powder with PEG400 had a sharp diffraction peak at 23.6 at˚20 which is evidence that Avicel PH101 remains in its crystalline step. the absence of characteristic peaks of Pioglitazone HCl in liquisolid system shows that Pioglitazone HCl is entirely converted into an amorphous or solubilized form. The absence of crystallinity in the liquisolid system is perhaps the result of solibilization in the liquid vehicle that is possibly absorbed and adsorbed on the carrier material (Avicel PH101) and coating material (Aerosil). we can verify the formation of a solid solution of Pioglitazone HCl inside the carrier matrix. The amorphization or solubilization of Pioglitazone HCl may result in an increase in the dissolution rate.

Differential scanning calorimetry (DSC)

Pioglitazone HCl peaks are clear in its thermogram demonstrating a sharp characteristic endothermic peak at 149.9˚C corresponding to its melting temperature, such sharp endothermic peak signifies that Pioglitazone HCl was used in pure crystalline state as shown Figure 5. The thermograms of Avicel PH101 displayed broad endothermic peak at 60.1˚C due to volatilization of adsorbed water and charring of the cellulosic material. The thermal behavior of aerosil 200 did not show any sharp peak, proving to be in an amorphous state. On the other hand, the LS thermogram displayed complete disappearance characteristic peaks of Pioglitazone HCl, so we can say that formation of drug solution which is molecularly dispersed within the LS matrix. That was accompanied by the formation of a new endothermic peak at 96.0˚C for PG and 62.3˚ for PEG 400 that indicates to the melting and decomposition of the whole LS. Such disappearance of the drug peaks upon formulation of the LS was surely indicating the formulation of an amorphous solid solution.

Stability Studies

Stability studies were conducted for the optimized formulation (LSI). Stability testing of drug products begins as part of the drug discovery process and ends with the rejection of the compound or its acceptance as a commercial product. The FDA and ICH specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The study was performed under stability conditions at 40^0C ± 2^0C/75% RH ± 5% RH for three months. The selected formulation stable without any appreciable change in postcompression evaluation parameters and drug release studies. Hence the formulation is further can proceed for *in vivo* studies.

CONCLUSION:

Pioglitazone HCI exhibits high permeability through biological membranes, but its absorption after oral administration is limited by its low dissolution rate due to its very low aqueous solubility. The aim of this study was to improve the dissolution rate of Pioglitazone HCI and thereby increase solubility. Hence, liquisolid technique and solid dispersion by solvent evaporation technique were chosen to enhance the dissolution rate of Pioglitazone.

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