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FORMULATION DEVELOPMENT, CHARACTERIZATION AND EVALUATION OF LIQUISOLID TABLET CONTAINING PIOGLITAZONE HCL

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ABSTRACT

The aim of present study was to improve the solubility of pioglitazone HCl a practically insoluble antidiabetic drug by using liquisolid technique. The in vitro release pattern of liquisolid tablets and directly compressed tablets were studied using USP-II apparatus. Different Liquisolid tablets were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and Sodium starch glycolate were employed as carrier, coating material and disintegrant respectively. The drug release rates of Liquisolid tablets were distinctly higher as compared to directly compressed tablets, which show significant benefit of Liquisolid tablets in increasing wetting properties and surface area of drug available for dissolution. The optimized formulation showed the higher drug release during ex-vivo and in-vivo study against conventional and marketed tablet preparation. The DSC and FT-IR studies conforms the no significant interaction between the drug and excipients used in Liquisolid tablets. From this study it concludes that the Liquisolid technique is a promising alternative and best suitable method for enhancing solubility of pioglitazone HCl.

Keywords: Pioglitazone HCl, Drug concentration, liquisolid tablets, new mathematical model, ex-vivo and in-vivo absorption.

INTRODUCTION

Prior to absorption into the systemic circulation orally administered drugs need to dissolve in the gastrointestinal fluids. This dissolution process mayact as absorption rate controlling step for hydrophobic drugs.[1]A most important parameter that is useful for 'poorly soluble' drugs is the dose: solubility ratio of the drug. The dose: solubility ratio can be defined as the volume of gastrointestinal fluids necessary to dissolve the administered dose. When this volume exceeds the volume of fluids available, one may anticipate incomplete bioavailability from solid oral dosage forms.[2]Increasing the dissolution and bioavailability of poorly soluble drugs is a major challenge facing the pharmaceutical industry today as about 40% of potential drugs produced are almost insoluble. There are many methods for increasing the dissolution of drugs such as reducing particle size, conversion of the drug to the salt form or polymorph, the use of complexing agents such as cyclodextrins, the use of surfactants or co-solvents and the synthesis of pro-drugs.[3]Over past few decades, various approaches have been introduced to solve the problem of formulation of poorly soluble drug substances, with the original seek of enhancing drug dissolution characteristics, with different degrees of success. The 'liquisolid technique' is a new and promising addition towards such a novel aim. The term "liquisolid systems" refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs, or drug suspensions or drug solutions of waterinsoluble solid drugs in suitable non-volatile solvent systems, into "dry" non-adherent, free-flowing and readily compressible powder admixtures by blending the suspension or solution with selected carriers and coating materials. The drug solution or suspension or may be liquid drug, called 'liquid medication' was converted into free flowing, non-adherent, readily compressible and dry looking powder by simple addition of selected

excipients, called carrier and coating materials. Microcrystalline Cellulose (Avicel PH 102) was used as carrier material because of porous nature and having good absorption properties for liquid medication. Silica powder (Aerosil 200) were used as coating material as it consists of very fine and highly adsorptive particles, which covers the wet carrier particles and shows dry-looking powder by adsorbing any excess liquid.[4,5]

Poorly water insoluble drug like carbamazepine, griseofulvin, naproxen, lansoprazole and famotidine found in liquisolid formulation. But enhancing the solubility of water insoluble drug, pioglitazone hydrochloride by developing new mathematical model is totally new. The goal of this study was to enhance the solubility of pioglitazone HCl,antidiabetic agent that have therapeutic dose of 15 – 45 mg as per BCS. It selectively stimulates nuclear receptor peroxisone proliferators-activated receptor gamma (PPAR-gamma).

MATERIALS AND METHODS

Materials: Pioglitazone was kindly gifted by Cadila Pharmaceuticals Ltd, (Ankleshwar, India). Avicel PH 102 (course granular microcrystalline cellulose) and Aerosil 200 (colloidal silicon dioxide) (Leben Pvt. Ltd. India), Sodium starch glycolate and Propylene glycol (Rajesh Chemicals Co. Mumbai, India) were used.Wistar albino rats were procured from our college and get the approval for animal study.

Application of the mathematical model for designing the liquisolid systems: In order to attain optimal pioglitazone HCl solubility in the liquisolid formulations, several factors were varied including the concentration of the liquid vehicle PG (15, 20, 25 and 30 % w/w), and the carrier: coat ratios (different R-values) (ranging from 30 to 50). For optimal flowability and compressibility of liquisolid tablets, the ‘‘new formulation mathematical model of liquisolid systems” was employed to calculate the appropriate quantities of excipients required to produce liquisolid systems of acceptable flowability and compressibility. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties.[5-7]Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used,

$$R = Q/q \quad \text{.....1}$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratioof the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolidsystem. i.e.

$$Lf = W/Q \quad \text{.....2}$$

Precompression studies: Prior to the compression of the formulations into tablets, compressibility, flowability, bulk density, tapped density, angle of repose, Carr’s compressibility index and Hausner’s ratio studies were carried out. To ensure the suitability of the selected excipients, various studies were performed on powder mass of liquisolid formulation including DSC and FT-IR.

Preparation of liquisolid tablets: The desired quantities previously weighed of the solid drug and propylene glycol was mixed as per references, (Table 1) until a homogenous drug solution was obtained. The resulting hot liquid medications were incorporated into the carrier material and then blended with the coating material.[4,5]Each liquisolid formulation containing 6% sodium starch glycolate were compressed into tablets.[5,8]

Quality control tests of the prepared tablets: The liquisolid tablets and conventional tablets were evaluated via quality tests which were conducted in accordance to the Indian and United state Pharmacopoeia specification. [9-11]Tablets were evaluated by carrying out tests for weight variation, uniformity of tablet thickness and diameter, friability, hardness, disintegration, dissolution, and content uniformity. All the tests were carried out in triplicate and according to the compendial specifications.**[10,11]** The dissolution test was used to compare between prepared liquisolid tablets and marketed tablets. The USP Apparatus II was used with 900 ml of 0.3 M KCl buffer solution (pH 2) at 37 ± 0.5^0 C, and the apparatus was run at 75 rpm. Five millilitre samples were withdrawn after 5, 10, 15, 30, 45, 60, 90 and 120 minutes and were compensated by equal amounts of the dissolution medium. The concentrations of pioglitazone HCl were determined spectrophotometrically at 230.4 nm. [12]

Ex-vivo absorption study: The ex-vivo absorption study of pioglitazone hydrochloride was determined by using a locally modified everted small intestinal sac technique, based on the apparatus of Crane and

Wilson (Figure 1) as modified by Crampton and Matthews. [13-14]

The fresh small intestine of sheep was washed with distilled water and with cold normal saline solution. The intestinal segment of 5 cm in length was cut from a specific region of intestine and everted with the help of glass rod. The distal end of the segment was tide and the optimized liquisolid tablet was placed in the sac containing 1-2 ml of phosphate buffer pH 7.2 from the proximal end which was attached to pipette. The pipette was adjusted to immerse the sac completely into the bottle containing 500 ml Kreb's mammalian ringer solution (mucosal solution). 5 ml of mucosal solution from the bottle was withdrawn at the various time intervals (5, 10, 15, 30, 45, 60, 90, 120 minutes). The aliquots were analyzedspectrophotometrically at 230.4 nm.

In-vivo study: An in-vivo evaluation study was performed on normal healthy Wistar albino rats. The experimental design was approved by Institutional Animal Ethical Committee and the study was performed on optimized liquisolid tablet according to the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines for the use and care of animals. [15]

Three groups of Wistar albino rats of either sex weighing 150 to 250 g each (4 in each group) that were fasted (with water) at 24 hours before the experiments. Diabetes was induced in the rats by administering alloxan monohydrate (120mg/kg) intraperitoneally into the 24 hours fasted rats. The rats had free access to standard laboratory feed and water and were keeping under standard laboratory conditions. Blood samples were collected after 48 hours and blood glucose levels were estimated. The blood glucose level for the control and test samples was determined with the help of instrument Auto Biochemical analyzer (Om Sai Clinical Lab).

RESULTS AND DISCUSSION

Application of the mathematical model for designing the liquisolid systems: In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ-values) of powder excipients were utilized. In propylene glycol, the U-value of Avicel PH 102 was found to be 0.16, while for Aerosil 200 the Φ -value used was equal to that of Cab- O-Sil M5 as they both possessed the same specific surface area and density,[16] the Φ -value of a powder material is a function of its specific surface thus, Aerosil 200 and Cab-O-Sil M5 are expected to have similar adsorptive power.[4, 5, 16] Therefore, the Φ -value used for Aerosil 200 in PG was 3.31. This relatively high Φ -value is advantageous as it results in smaller sizes of the formulated tablets (4-5).Using ''the new formulation mathematical model", the straight line equation for Avicel PH 102 and Aerosil 200 in PG would be

$$Lf = 0.16 + 3.31(1/R) \quad \text{.....3}$$

For each R-value used, the corresponding Lf value can be calculated. Table 1 represents the exact qualitative and quantitative composition for each formula.

Precompression studies of the prepared liquisolid powder system: The flow property depends on particle size, particle shape, porosity and density of bulk powder. Irregular flow of powder from the hopper produces tablet with nonuniform weights. The effect of liquid load factor (L_f), which is a ratio of mass of liquid (PG) added to the mass of Avicel PH 102 on flowability and compressibility of the final admixture of the powder. The liquisolid tablet with higher carrier to coating ratio (R), contained the less amount of liquid medication with high amount of carrier material and less amount of coating material. [17] The liquisolid tablet formulation with increasing R-value in the range from 30 to 50 i.e. decrease the volume of liquid medication resulted in the increasing in flowability of the final admixture. This resulted in to decreasing in the angle of repose. With the increase in the R-value, which result in to decreasing in the liquid load factor (Lf). With decrease in L_f value flow property was found to be increase. It also resulted in an increase in the compressibility of final admixture.

In general, value of bulk density less than 1.2 g/cm^3 indicates good packing. The angle of repose greater than 40^o has very poor flow properties whereas minimum angle close to 20^o correspond to very excellent flow property. Powders showing Carr's index up to 21 are considered of acceptable flow property and Hausner's ratio values less than 1.25 indicate good flow properties (Table 2).

Formulation LS3, LS4, LS8, LS9, LS10 and LS12 were proven to be excellent flowing property according to angle of repose, Carr's index and Hausner's ratio. Formulae LS1, LS2, LS5 and DCT were proven to be acceptably flowing properties. Liquisolid tablet formulation, LS3 was found best and optimized formulation with acceptable flowability according to the angle of repose[11-12] and subjected for further evaluation such as ex-vivo absorption and in-vivo pharmacokinetic study.

The sample of pure pioglitazone and optimized LS3 formulation were subjected to FT-IR spectroscopy analysis, and their spectra over the frequency range between 4000 and 600 cm^{-1} and at 1 cm^{-1} resolution are shown in Figure 2. It gives the distinct picks which matches the peaks of plain pioglitazone. Figure 3 showed the thermal behaviour of pure pioglitazone HCl and optimized LS3 formulation. Pioglitazone HCl exhibits a sharp melting endotherm with onset temperature 192.13 ^0C and peak temperature 193.88 ^0C.

Quality control tests: The thickness, hardness, friability, weight variation and disintegration time of the prepared liquisolid tablets shown in Table 3. Due to the varying tablet weight, the investigated powder blends were compressed into different thickness and hardness. The investigated formulation complied with the British and United state Pharmacopoeias. All the selected pioglitazone liquisolid tablets had acceptable friability as none of the investigated tablet had the percentage loss in tablets weight not more than 1%, and also not a single tablet was broken. The tablet also having sufficient hardness, uniformed drug content and disintegration time less than 5 minutes due to the maximum amount of microcrystalline cellulose as compared to aerosil 200, which is also used as a tablet binder and disintegrants. [11-12]

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets; it was observable that formulae LS3, LS7, LS10, LS11 and LS12 complied with the test of pioglitazone hydrochloride content uniformity according Indian Pharmacopoeias specification (90%-110%), having the average pioglitazone hydrochloride content of 92.97 %, 94.18 %, 92.31 %, 94.30 % and 95.84 % w/w respectively. In each of the mentioned formulae, no more than one tablet is outside this limit nor is one individual outside the limits of 90-110 %. The more uniform pioglitazone hydrochloride content in the formulae LS3, LS7, LS10, LS11 and LS12 may be due to fact that, these formulae have high R-values of 50, 30, 30, 40 and 50 respectively. Due to such high R-values represent higher Avicel PH 102 (carrier) concentration that might lead to a more uniform distribution of the drug by either adsorption onto or absorption into carrier, therefore having more homogeneous distribution throughout batch.

The results of in vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles. All the liquisolid tablets showed higher drug release than the directly compressible tablet (DCT) and marketed preparation. The enhanced dissolution rates of liquisolid tablets compared to DCT and marketed preparation may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica).Thus, its release is accerlated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid tablets. PG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.

The comparative release of 15, 20, 25,and 30 mg pioglitazone hydrochloride tablet from LS1-LS3, LS4-LS6, LS7-LS9, LS10-LS12, MRKT and DCTP1, DCTP1, DCTP2, DCTP3, DCTP4, formulations are plot as cumulative percentage release Vs time in figure no. 4.

Ex-vivo absorption study: The ex-vivo gastrointestinal absorption study of pioglitazone HCl optimized batch (LS3) has been carried out using the modified Wilson and Crane model design in laboratory level. The figure no. 5 indicating the percentage of drug absorbed in GI region with respect to time. The enhanced dissolution rates of optimized liquisolid formulation (LS3) may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica).Thus, its release is accerlated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid tablets.The dissolution is the rate determining step in the drug absorption in gastrointestinal tract.Due to increasing in the dissolution of pioglitazone HCl in optimized LS3 formulation, it is concluded that, the absorption of the pioglitazone HCl from gastrointestinal region also increase.

In-vivo study: The in-vivo efficiency of the optimized liquisolid formulation (LS3) of pioglitazone HCl was performed on healthy normal Wistar albino rats by measuring the hypoglycemic effect (Reduction in glucose level) produced after oral administration. The optimized liquisolid formulation of pioglitazone hydrochloride was administered by preparing a suspension of tablet in 3 ml distilled water to the one group. The other group received the marketed pioglitazone hydrochloride

tablet in the same manner as described above. When the suspension of LS3 formulation was administered, a rapid decreasing in the blood glucose level was observed within the two hour after oral administration as compared to the marketed formulation. (Figure no.6).

The decreasing in the blood glucose level as compared to marketed formulation, is due the fact that increasing in the solubility and absorption of the drug. It was found that the relative bioavailability of pioglitazone HCl from the liquisolid tablet was significantly higher than that from the commercial tablets. The increase in insulin blood level was more pronounced with the liquisolid tablets than with the commercial tablets indicating a higher bioavailability from the liquisolid compacts. These partially contrary results of bioavailability of liquisolid formulations shown that still more in vivo data is needed to confirm the superiority of liquisolid compacts.

CONCLUSION

The solubility of pioglitazone hydrochloride was increased by dispersing the drug into the propylene glycol, which in terms increase the wetting property and surface area of drug particle and hence improve the dissolution and oral bioavailibity of the drug.The FT-IR spectra revealed that, there was no interaction between the drug and excipients. The in-vitro drug release of pioglitazone hydrochloride liquisolid tablet showed increase in dissolution rate of pioglitazone HCl as compared to the directly compressible and marketed tablets.The *ex-vivo* absorption study of optimized LS3 formulation using modified Wilson and Crane apparatus shows the significant drug absorption through the small intestine of sheep.The *in vivo* reduction of blood glucose level through the optimized formula LS3 is greater than that of marketed preparation this is due to the increase in solubility results in fast dissolution of drug and rapid absorption.

Table 1: The composition of different pioglitazone liquisolid system.

Formulation code	Cd in % w/w	R	Lf	Q (g)	q (g)	6 % SSG (g)	Unit dose weight (g)
LS1		30	0.270	0.425	0.014	0.033	0.487
LS2	15	40	0.243	0.473	0.011	0.041	0.540
LS3		50	0.226	0.508	0.010	0.044	0.577
LS4		30	0.270	0.444	0.014	0.040	0.518
LS5	20	40	0.243	0.493	0.012	0.043	0.568
LS6		50	0.226	0.530	0.010	0.046	0.606
LS7		30	0.270	0.462	0.015	0.042	0.544
LS8	25	40	0.243	0.514	0.012	0.045	0.596
LS9		50	0.226	0.553	0.011	0.048	0.637
LS10		30	0.270	0.481	0.016	0.043	0.570
LS11	30	40	0.243	0.534	0.013	0.047	0.624
LS12		50	0.226	0.575	0.011	0.050	0.666

cd: drug concentration in liquid, Lf: liquid load factor, Q: carrier material, q: coating material, SSG: sodium starch glycolate.

Table 2: Results of flowability parameters of different liquisolid formulations

Formulation Code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
LS1	0.5980	0.7475	30.10	20.00	1.25
LS2	0.5763	0.7044	30.18	18.18	1.22
LS3	0.5215	0.5650	30.14	07.69	1.08
LS4	0.6140	0.6822	30.31	10.00	1.11
LS5	0.6420	0.8025	30.02	20.00	1.25
LS6	0.5085	0.5933	30.14	14.28	1.16
LS7	0.6977	0.7850	30.31	11.11	1.12
LS8	0.4973	0.5738	29.98	13.33	1.15
LS9	0.5178	0.6061	29.94	14.28	1.16
LS10	0.5453	0.6445	29.94	15.38	1.18
LS11	0.5128	0.5983	30.06	14.28	1.16
LS12	0.4737	0.5414	29.98	12.50	1.14

Table 3: Evaluation parameters of liquisolid Tablets

Liquisol tablet	Tablet dimension		Hardness (N)*	Friability		Weight variation (g)*	Mean disintegration time (minutes)
	Thickness (mm)*	Diameter (mm)*		Fines (%)	No. Of broken tablets		
LS1	3.27 ± 0.03	12.1 ± 0.00	54.4 ± 2.05	0.4166	None	0.481 ± 0.024	4.18 ± 0.07
LS2	3.58 ± 0.19	12.1 ± 0.00	49.2 ± 1.47	0.3636	None	0.550 ± 0.027	4.34 ± 0.04
LS3	4.00 ± 0.00	12.1 ± 0.00	49.0 ± 1.96	0.3424	None	0.581 ± 0.028	4.30 ± 0.09
LS4	3.43 ± 0.03	12.1 ± 0.00	54.1 ± 1.17	0.7812	None	0.515 ± 0.025	4.37 ± 0.02
LS5	3.73 ± 0.02	12.1 ± 0.00	51.9 ± 0.98	0.3676	None	0.586 ± 0.028	4.11 ± 0.10
LS6	4.07 ± 0.06	12.1 ± 0.00	48.3 ± 1.47	0.3389	None	0.616 ± 0.030	4.33 ± 0.05
LS7	3.66 ± 0.02	12.1 ± 0.00	50.6 ± 1.17	0.3787	None	0.548 ± 0.027	3.43 ± 0.05
LS8	4.09 ± 0.02	12.1 ± 0.00	49.2 ± 1.47	0.6644	None	0.608 ± 0.029	3.22 ± 0.08
LS9	4.32 ± 0.00	12.1 ± 0.00	51.2 ± 1.47	0.5988	None	0.638 ± 0.031	2.48 ± 0.08
LS10	4.00 ± 0.00	12.1 ± 0.00	47.0 ± 0.98	0.7168	None	0.571 ± 0.028	2.38 ± 0.06
LS11	4.31 ± 0.02	12.1 ± 0.00	44.1 ± 1.17	0.6451	None	0.628 ± 0.031	2.47 ± 0.06
LS12	4.53 ± 0.03	12.1 ± 0.00	47.0 ± 0.98	0.5934	None	0.666 ± 0.033	2.21 ± 0.09

*All values are expressed as mean ± SD (n=3)

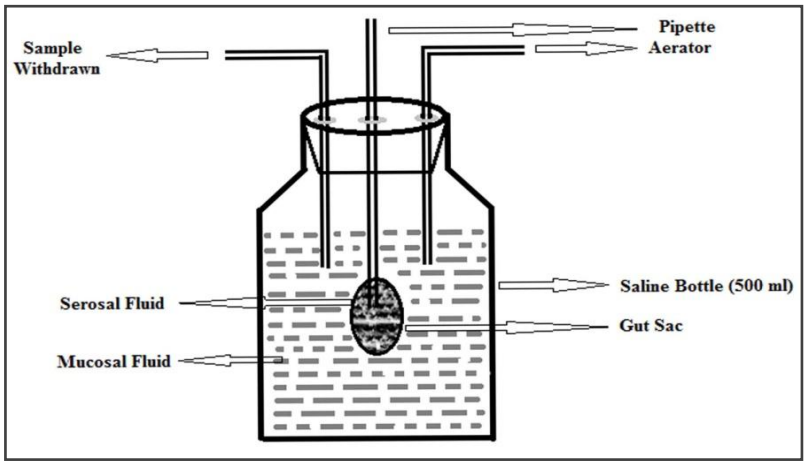

Figure 1: Modified Wilson and Crane apparatus.

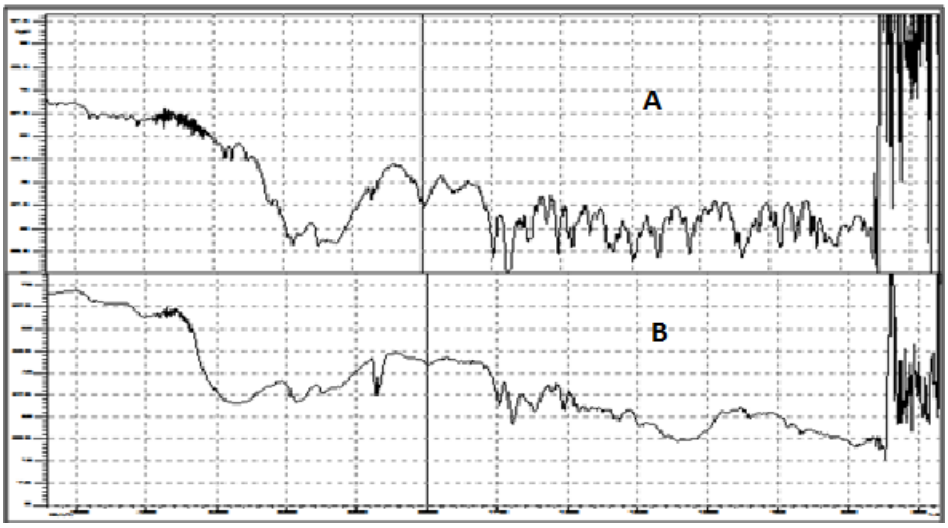

Figure 2: A- FT-IR spectra of pioglitazone HCl, **B**-FT-IR spectra of liquisolid tablet powder mixture.

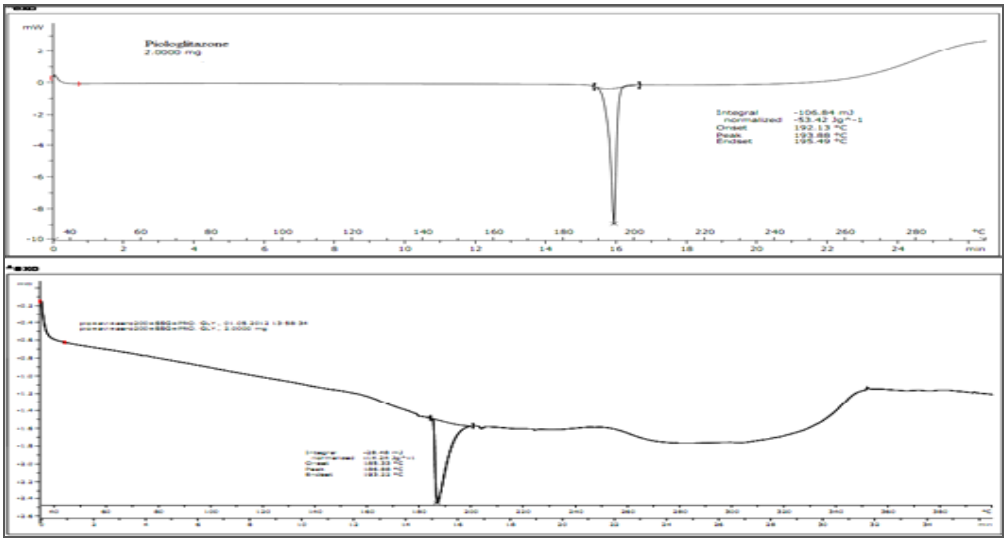

Figure 3: DSC thermogram of pure pioglitazone HCl and optimized LS3 formulation

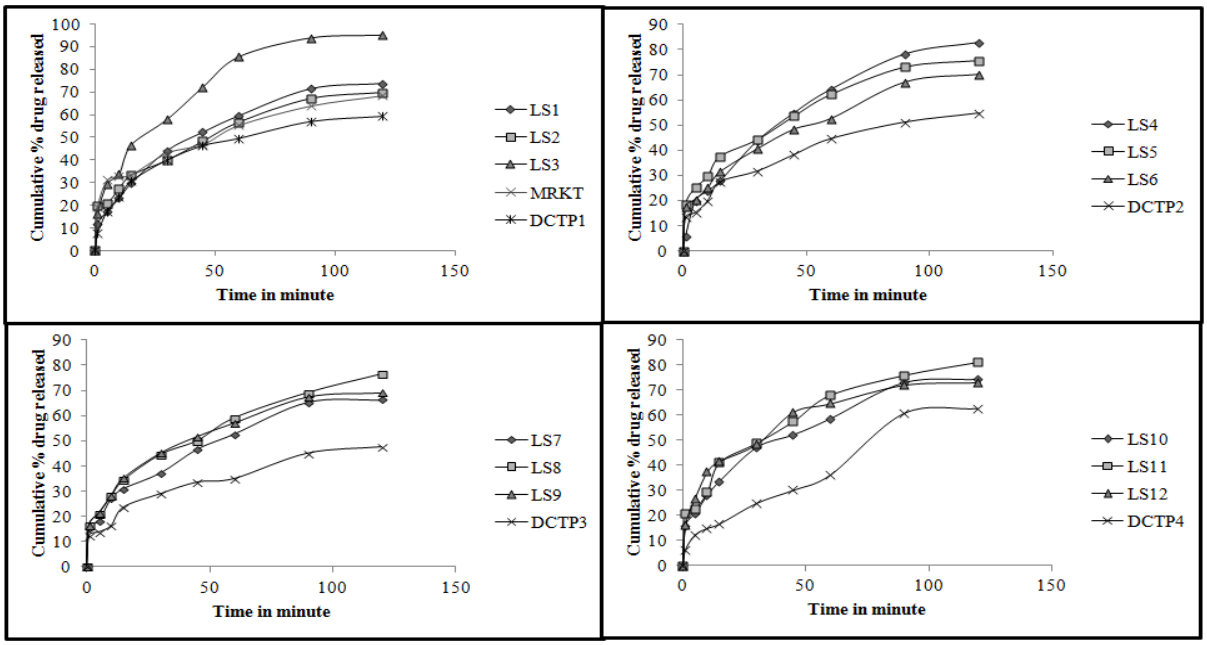

Figure 4: Dissolution profile of liquisolid formulations

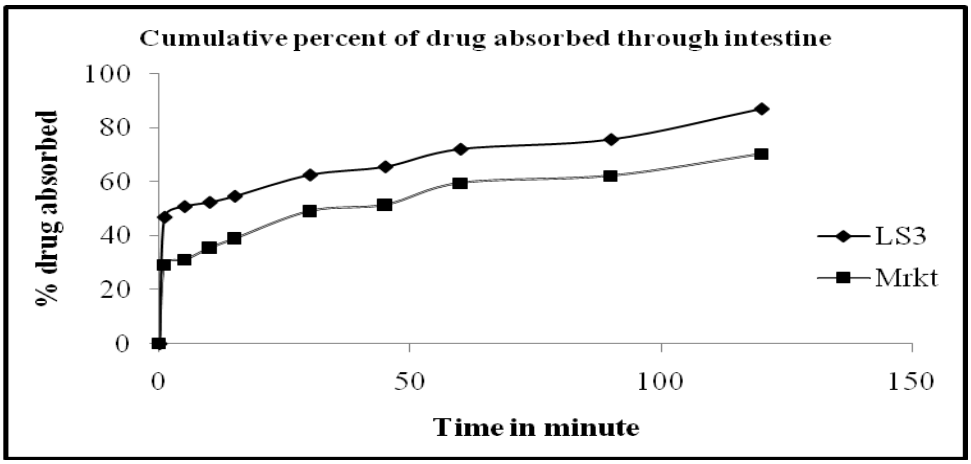

Figure 5: Intestinal absorption of pioglitazone hydrochloride.

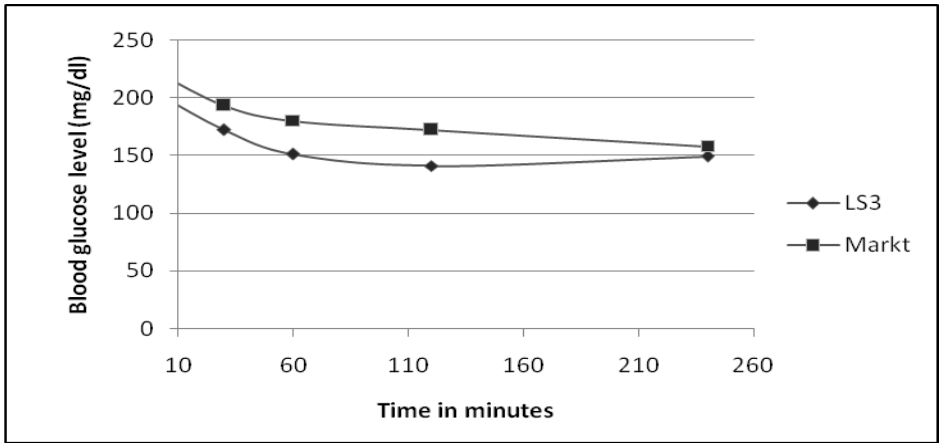

Figure 6: Reduction in blood glucose level in Wistar albino rats.

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