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Improved Dissolution Time and Oral Bioavailability of Pioglitazone Using Liquisolid Tablets: Formulation, *In Vitro* Characterization, and *In Vivo* Pharmacokinetics in Rabbits

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Cite This: *ACS Omega* 2024, 9, 42687−42697

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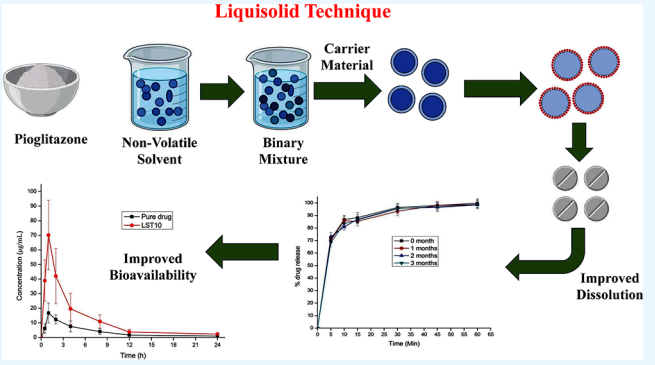
ABSTRACT: In the current study, it was intended to prepare liquisolid tablets of pioglitazone HCl to improve the bioavailability and dissolution time of the drug, as it has low solubility in water. Mathematical formulas were adopted, and the quantities of the carrier (MCC), coating material (colloidal silicon dioxides), and nonvolatile liquid vehicle (Tween 80) were taken. Various ratios of the drug to liquid and carrier to coating had been used in the formulation of liquisolid compacts. The evaluation of the formulated liquisolid compacts was done by performing FTIR, DSC, XRD, and SEM studies. Postcompression parameters, dissolution, stability, and bioavailability were accessed for the optimized formulation. FTIR and DSC studies showed the compatibility of the drugs and excipients. XRD revealed the transition to the amorphous state. It was found that the properties of the newly manufactured liquisolid tablets were within the parameters of what is considered acceptable. The optimized formulation of LST10 showed 99.87 ± 0.19% ($p < 0.05$) pioglitazone released within 60 min of dissolution. Dissolution data treatments (Q_{15}, IDR, RDR, %DE, MDT, f_1, and f_2) resulted in better drug release than other drugs studied and marketed tablet formulations. The optimized formulation produced had been proven stable when it was subjected to accelerated stability testing. This suggested that the bioavailability of pioglitazone was enhanced, as indicated by the substantial increase in AUC_{0-t} (3.06-fold) and C_{max} (4.18-fold). According to the findings, the selected combination and method significantly increased the dissolution time and bioavailability of pioglitazone. Moreover, this developed method can be used for other drugs with low water solubility.



1. INTRODUCTION

Drugs with poor aqueous solubility are a limiting factor in developing new formulations.[1] Absorption would be limited due to the rate of dissolution, resulting in poor and fluctuating oral bioavailability. Therefore, pharmaceutical researchers are required to develop processes that are reliable, efficient, stable, safe, cost-effective, and reproducible to enhance the aqueous solubility of the medications, which is categorized in the Biopharmaceutical Classification System (BCS) class II.[2]

Pioglitazone is a PPARγ agonist. It is a BCS class II drug with an aqueous solubility of 0.015 mg/mL. It is commonly prescribed by the physicians for the treatment of type II diabetes mellitus.[3,4] In recent years, it has been repurposed against hepatitis C virus[5] and Alzheimer's disease.[6] However, this particular drug has low and incomplete release, which adversely affects its bioavailability. It is a water-insoluble drug (0.015 mg/mL). It is also a weak base with a pK_a value of 7.4 and a log P value of 2.3 with the absolute bioavailability of 83%.[4] Various techniques have been employed to enhance its solubility. Solid dispersions[7,8] and inclusion complexes[9] have gained popularity among the researchers, but their commercial utility is extremely limited due to several factors including poor stability, recrystallization, and a lack of understanding of solid-state structures. Nanocrystallization,[10] nanosuspension,[11] electrospinning, and electrospraying methods[12] are approaches to enhance the dissolution rate, but they require advanced and sophisticated technology with high production cost. Cosolvent solubilization is a primary approach to solubilize a poorly aqueous drug.[13] However, its potential application in formulation development is extremely limited. None of the previous techniques developed produced a complete product of pioglitazone. Due to this, an advanced technique that can

Received: November 16, 2023
Revised: August 18, 2024
Accepted: August 27, 2024
Published: October 8, 2024

improve the dissolution of pioglitazone through liquisolid has been introduced. However, as of now, this method has been demonstrated in the *in vitro* studies only; thus, it is lacking of *in vivo* evaluation and the establishment of IVIVC (*in vitro*−*in vivo* correlation).[14,15] Furthermore, there is a need for extensive evaluation of the developed formulation and to optimize it. In the liquid−solid technique, poor aqueous soluble drugs are dissolved in a nonvolatile solvent. To make it dry and nonadhesive, it is loaded on the carrier with a coating material. It is also easier for the punching machine to compact the drug powder. Furthermore, this particular technique helps to wet and dissolve the drug, which leads to an increase in its bioavailability when it is taken orally.[16,17] The technique has many advantages including great industrial potential, simple processing stages, and low cost.[16−18] Various investigators have proven in their studies to increase the dissolution rate and bioavailability of glyburide,[18] telmisartan,[19] atorvastatin,[20] and efavirenz[17] by using the liquisolid technique. Hence, this study aims to design and evaluate the liquisolid tablets prepared from the binary solid dispersions of pioglitazone HCl using FDA-approved excipients to improve the drug's solubility, dissolution, and bioavailability.

2. MATERIALS AND METHODS

2.1. Materials. Aurobindo Pharma Ltd. located in Hyderabad, India, had provided the pioglitazone HCl used in this study. The following excipients, namely, polyethylene glycol 400 (PEG 400) (Otto Chemicals, Mumbai), Tween 80, propylene glycol (PG), Span 80 (Finar Chemicals Ltd., Ahmedabad), and microcrystalline cellulose (MCC) (Chemika-Biochemica-Reagents, Mumbai) were purchased. Meanwhile, colloidal silicon dioxides, sodium starch glycolate (SSG), crospovidone, and Cremophor RH 40 were received as gift samples from Yarrow Chem Products, Mumbai. A conventional Pioglit 15 tablet (Sun Pharma Laboratories Ltd., Sikkim, India; batch no. GTD1065A; manufacturing date: June 2022 and expiry date: May 2024) was purchased from the Indian market.

2.2. Solubility Study. The solubility study was performed to screen the nonvolatile solvents. Two mL each of PG, PEG 400, Cremophor RH 40, Tween 80, and Span 80 was taken as nonvolatile solvents in different screw-capped vials. The excess amount of the drug was added to all of the solvents to determine the solubility. These vials were kept on a water bath shaker (Remi Elektrotechnik Ltd.) for 72 h at 37 ± 2 °C. At equilibrium, vials containing drug solvent mixtures were transferred into the test tubes and centrifuged (KEMI, Kerala) for 20 min at 6000 rpm. The supernatant was filtered through a 0.45 μm Millipore filter (Spectrum Medical, Inc., San Diego, CA), diluted with methanol, and analyzed by a UV−vis spectrophotometer (Shimadzu, model UV-1900i, Japan) at 270 nm[21] against a blank (the blank sample contained the same concentration of the specific solvent without the drug).

2.3. Preparation of Binary Systems. Pioglitazone HCl and various solvents (nonvolatile), namely, PG, PEG 400, and Tween 80, at 1:0.5, 1:1, and 1:1.5 weight ratios were kneaded for 10 min in a glass mortar and pestle to prepare the liquid form of the drug based on their solubility. A solubility study was performed for the developed binary formulations to screen the best possible combinations for the liquisolid system. The formulation design of the binary system is shown in Table 1.

2.4. Characterization. *2.4.1. Fourier Transform Infrared Spectroscopy (FTIR).* Pure pioglitazone, excipients, and optimized formulations (2−5 mg) were placed on the diamond ATR of an FTIR spectrophotometer (model Cary 630, Agilent Technologies, Germany). These were scanned at the 650−4000 cm^{-1} range.[22,23]

2.4.2. Differential Scanning Calorimetry (DSC). A DSC instrument (Pyris, PerkinElmer, Singapore) was used to record the thermograms of the drug, excipients, binary systems, and the optimized liquisolid formulation. The thermograms were recorded in the range of 35−250 °C (10 °C/min) by using a nitrogen atmosphere (150 mL/min). Alpha alumina powder was employed as a standard material in the platinum crucibles for this study.[22,23]

2.4.3. X-ray Diffraction (XRD) Study. To verify the crystallinity of the drug, binary systems, and the optimized liquisolid formulation, an XRD instrument (Ultima III, Rigaku, Japan) was used. During the analysis of the samples, the XRD device was operated at 25 °C with a voltage of 40 kV and a current of 30 mA. Then, the samples were evaluated in the range of 5−50° from 2θ and counted at a rate of 0.4 s/step.[21,23]

2.4.4. Scanning Electron Microscopy (SEM) Study. Pioglitazone HCl, binary systems, and the optimized liquisolid formulation were subjected to SEM (JSM6360, Jeol, UK) analysis to understand their surface morphologies. The operating conditions for this study were maintained at a 20 kV accelerating voltage and at a 45 nA probe current for 60 s.[22,23]

Table 1. Formulation Design of Binary Systems of the Pioglitazone for the Development of the Liquisolid Compact

formulation	nonvolatile solvent	pioglitazone HCl:nonvolatile solvent	kneading time (min)
BS1	PEG 400	1:0.5	10
BS2		1:1	
BS3		1:1.5	
BS4	PG	1:0.5	
BS5		1:1	
BS6		1:1.5	
BS7	Tween 80	1:0.5	
BS8		1:1	
BS9		1:1.5	

2.5. Formulation of Liquisolid Tablets. *2.5.1. Mathematical Approaches for the Calculation of Optimum Quantities of the Carrier and Coating Material.* Solid-state characterization of BS5 and BS8 formulations showed better drug release. Therefore, these systems were utilized for the formulation of liquisolid compacts. The selection of the amount of carrier and coating materials played an important role in the effective formulation of liquisolid compacts. In this regard, the liquid loading factor (L_f) and carrier ratio were used to determine the appropriate amount of carrier and coating materials (Trucillo, 2022). MCC and colloidal silicon dioxide were selected as the carrier and coating material, respectively. MCC and colloidal silica were added to the selected binary mixture and triturated with a porcelain mortar. The angle of repose was measured after every successive addition. The addition of the carrier and the coating material was continued until an acceptable flow property was achieved. L_f was determined by employing formula 1 shown below.[16]

https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697

Table 2. Formulation Design of Pioglitazone HCl Liquisolid Powder[a]

formulation code	pioglitazone HCl (mg)	PG (mg)	Tween 80 (mg)	L_f	MCC (Q) (mg)	colloidal silicon dioxide (q) (mg)	SSG (mg)	crospovidone (mg)	unit dose weight (mg)
LST1	15	15		0.2	150	7.5	0.937 (0.5%)		188.437
LST2	15	15		0.2	150	7.5	1.875 (1%)		189.375
LST3	15	15		0.2	150	7.5	2.812 (1.5%)		190.312
LST4	15	15		0.2	150	7.5		0.937 (0.5%)	188.437
LST5	15	15		0.2	150	7.5		1.875 (1%)	189.375
LST6	15	15		0.2	150	7.5		2.812 (1.5%)	190.312
LST7	15		15	0.2	150	7.5	0.937 (0.5%)		188.437
LST8	15		15	0.2	150	7.5	1.875 (1%)		189.375
LST9	15		15	0.2	150	7.5	2.812 (1.5%)		190.312
LST10	15		15	0.2	150	7.5		0.937 (0.5%)	188.437
LST11	15		15	0.2	150	7.5		1.875 (1%)	189.375
LST12	15		15	0.2	150	7.5		2.812 (1.5%)	190.312

[a]R = 20; batch size = 100 tablets.

$$L_f = \frac{W}{Q} \quad (1)$$

In this equation, W represents the weight of the liquid medication, while Q represents the weight of the carrier material.

The value R (excipient ratio) was measured by using formula 2:

$$R = \frac{Q}{q} \quad (2)$$

In this equation, Q represents the weight of the carrier material, while q represents the weight of the coating material.

2.5.2. Preparation of Liquisolid Powder. Selected BS5 and BS8 were taken to a porcelain mortar and kneaded for 10 min to obtain the viscous paste. Previously calculated quantities of carrier and coating materials were added to the mortar with continuous mixing. The above mixture was spread uniformly in the mortar surface and left for 15 min. During this period, the carrier and coating materials absorbed the liquid present in the formulation. After 15 min, the liquid−solid powder mixture was scratched with an aluminum spatula. Then, super disintegrants (SSG and crospovidone, 1, 2.5, and 5% w/w) were added to the mixture and mixed homogenously for 5 min.[17,18,20] Afterward, the liquid powders were subjected to the precompression parameters. The design of liquisolid formulations is shown in Table 2.

2.5.3. Precompression Parameters of Pioglitazone HCl Liquisolid Powders. The following precompression parameters, namely, the angle of repose and bulk and tapped density along with Carr's index (CI) and Hausner's ratio (HR) of pioglitazone HCl liquisolid powders, were determined as part of the precompression evaluation parameters.[24]

2.5.4. Compression of Pioglitazone HCl Liquisolid Tablets. The formulation of tablets was done by a rotary 10-station tablet punching machine that employed a compression technique with 8 mm round, concave punches, and they were further subjected to postcompression evaluation tests.[25]

2.5.5. Postcompression Parameters of Prepared Pioglitazone HCl Liquisolid Tablets.[26,27] *2.5.5.1. Thickness.* A calibrated Vernier caliper (maker: Mitutoyo, model 530119) was used to measure the thickness of the tablets (10 tablets). The tablets' thickness was controlled within a ±5% variation.

2.5.5.2. Hardness. A Monsanto hardness tester (model VMT) was used to measure the force required to break the tablets. Five tablets were taken randomly to test the hardness (IP), and the mean hardness was expressed in kg/cm^2.

2.5.5.3. Friability. A Roche friabilator (maker: Panomex, Inc., model PX/FTA-903) was used in the study to determine the friability of the tablets. Once the tablets were weighed (W_1) and placed into the friabilator chamber, the initial weight of the tablets was set at 6.5 g. Then, the tablets were placed in a friabilator chamber. The tablets had 4 min to roll and free-fall from a height of 6 in. inside the friabilator chamber while the rotation speed was set at 25 rpm. The tablets were collected and reweighed collectively (W_2). The % friability was determined using formula 3.

$$\% \text{ friability} = \frac{W_1 - W_2}{W_1} \times 100 \quad (3)$$

2.5.5.4. Weight Variation. Twenty tablets from each formulated batch were individually and randomly weighed in to determine the weight variation.

2.5.5.5. Drug Content. According to the IP procedure, 10 tablets were randomly selected to perform an evaluation of the drug content of the formulated tablets. Each tablet was crushed, and 10 mg of drug equivalent formulation was placed into the 10 mL volumetric flak. A small amount of methanol was added to solubilize it, and the volume was made up to 10 mL by adding 0.1 N HCl. It was shaken for 6 h in a horizontal shaker (model RSB12, Remi Elektrotechnik Ltd., India) at room temperature followed by sonication (Scientech SE-366) for 10 min. The solution was filtered through a 0.45 μm membrane filter (Millipore). The collected samples were analyzed at 270 nm by a UV−vis spectrophotometer (Shimadzu, model UV-1900i, Japan).

2.5.5.6. In Vitro Disintegration Time. A disintegration test apparatus (maker: Panomex, Inc., model PX/DTA-1901) was used as per the IP specifications. Disintegration was performed using 0.1 N HCl at 37 ± 2 °C as the immersion liquid. The disintegration time of the tablets in the apparatus was recorded.

https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697

2.5.5.7. In Vitro Dissolution Studies. Developed liquid formulations were studied for pioglitazone release in triplicate. In the dissolution experiments (Electrolab, model EDT-08Lx), 900 mL of 0.01N HCl was used as a dissolution medium maintained at a temperature of 37 ± 0.5 °C with a paddle rotation speed of 75 rpm. Following that, the samples were withdrawn at 5, 10, 15, 30, 45, and 60 min and maintained in sink conditions by adding 5 mL of the freshly prepared 0.1 N HCl. Postfiltration (0.45 μm, Millipore), the collected samples were analyzed at 270 nm by a UV−vis spectrophotometer (Shimadzu, model UV-1900i, Japan).

2.5.5.8. Dissolution Data Treatment. Dissolution data of pioglitazone HCl, optimized liquisolid formulation, and marketed formulations were determined considering various parameters.

The following is formula 4 that was used to measure the dissolution efficiency (DE).[27]

$$\mathrm{DE} = \frac{\int_0^t y\ \mathrm{d}t}{y_{100}t} \times 100\% \tag{4}$$

Here, y represents the area under dissolution, t represents 15 and 30 min, and y_{100} represents 100% dissolution in time t (15 and 30 min).

From the dissolution data, we were able to estimate the (Q_{15}) percentage of drug that was released after 15 min and the (IDR) first dissolution rate. The ratios of IDR of the optimized formulation, marketed formulation, and pure drug were plotted to calculate the (RDR) relative dissolution rate of pioglitazone HCl.

f_2 refers to the similarity factor[28] that was also calculated by formula 5.

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \tag{5}$$

In this equation, R_t and T_t are the dissolution rates of standard and test products, respectively, at time t.

2.6. Stability Study. Accelerated stability of LST10 was performed as per ICH Q1AR2 in triplicate. The LST10 was stored in a stability chamber (Hally Instruments, Mumbai, India) at 40 ± 2 °C maintaining 75 ± 5% RH for a 3-month time frame. At 1, 2, and 3 months, the samples were periodically analyzed for a hardness, disintegration time, and dissolution study, which was done at 5, 10, 15, 30, and 60 min.

2.7. Pharmacokinetic Study. A valid and verified method to estimate the pioglitazone from plasma was demonstrated (Figure S1 and Table S1) by an HPLC instrument (Infinity 1220 series, EZChrom Elite software, Agilent Technologies, USA).[9,28]

2.7.1. Animal Study. An *in vivo* study was done by following the approved (approval no. 02/IAEC/CIPS/2016−17, issued on 13th July, 2017 approved by IAEC, Chalapathi Institute of Pharmaceutical Sciences, Andhra Pradesh, India) guidelines. A similar study was performed earlier by our team.[21] In short, male New Zealand rabbits (6, with an average body weight of 1.75 ± 0.05 kg) were divided into a group of two (n = 3). The drug sample was prepared by dispersing 2.5 mg/mL pioglitazone with 0.5% methylcellulose. A similar sample was also prepared for LST10. The drug was administered orally to the experimental animals at an equivalent dose of 2.5 mg/kg per body weight.[29] Blood was collected from the experimental animals at 0.5, 1, 2, 4, 8, 12, and 24 h via a marginal ear vein. The blood was mixed with EDTA to avoid coagulation. The plasma was separated from the blood by centrifugation at 5000 rpm for 10 min and freeze-thawed at −80 °C until the analysis was done.

2.7.2. Sample Preparation. The freeze-thawed plasma samples were exposed to an ambient temperature before extraction. The samples were processed according to optimized methodologies reported earlier, and the samples were analyzed by verified methods using HPLC.[9,28]

2.7.3. Pharmacokinetic Analysis. Various pharmacokinetic parameters including C_{max}, T_{max}, $AUC_{0-\infty}$, and AUC_{0-t} from the plasma were estimated using the software program PK Solver.[30]

2.8. Statistical Analysis. All of the mean values were presented with their standard deviations (means ± SD). The statistically significant difference was determined using ANOVA/t tests at a 0.05 level of significance.[12,29]

3. RESULTS AND DISCUSSION

3.1. Screening of Nonvolatile Solvents. *3.1.1. Solubility Studies.* In liquisolid systems, the solubility of the liquisolids is an important factor. The greater the solubility of a drug in a liquid vehicle, the higher its dissolution rate, as the drug is comparatively more molecularly dispersed. Table 3 presents the details concerning the saturation solubility of pioglitazone HCl in the range of nonvolatile liquids. Pioglitazone HCl seemed to be more soluble in PEG 400 compared to other vehicles. The PEG 400 (6.63-fold) and PG (6.11-fold) showed more solubility than distilled water (13.77 μg/mL) (Table 3). This might be due to lowering of the surface tension and wetting of the drug molecule (Kim, 2015). Tween 80 and Span 80 showed almost similar fold of more solubility enhancement (4.90-fold). Meanwhile, Cremophor RH 40 had the least solubility among the entire selected vehicle. Due to this, PEG 400, PG, and Tween 80 were selected for further study. The enhancement of solubility of pioglitazone HCl might be due to the hydrophilic and lipophilic nature of the vehicle.

Table 3. Solubility of Pioglitazone HCl in Different Nonvolatile Solvents[a]

nonvolatile solvent	solubility (μg/mL)
PG	84.20 ± 3.27
PEG 400	91.25 ± 3.16
Tween 80	67.59 ± 2.89
Span 80	65.70 ± 4.17
Cremophor RH 40	54.47 ± 4.04
distilled water	13.77 ± 3.77

[a]Values are expressed as means ± SD, n = 3.

3.2. Preparation of the Binary System. The drug was converted into liquid using PEG 400, PG, and Tween 80 as nonvolatile solvents. The kneading technique for 10 min was utilized for the preparation of adopting various weight ratios (1:0.5, 1:1, and 1:1.5). Nine formulations (BS1−BS9) were formulated (Table 1) and characterized.

3.3. Characterization. *3.3.1. Optimization of the Drug and Nonvolatile Solvent Ratio.* Figure 1 exhibits the findings of the solubility of the developed binary systems (BS1−BS9). The formulations BS1−BS3, which contained PEG 400, had solubilized 32−89% of pioglitazone. In comparison to BS1 and BS2, a 1:1.5 weight ratio (BS3) showed a significant difference

https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697

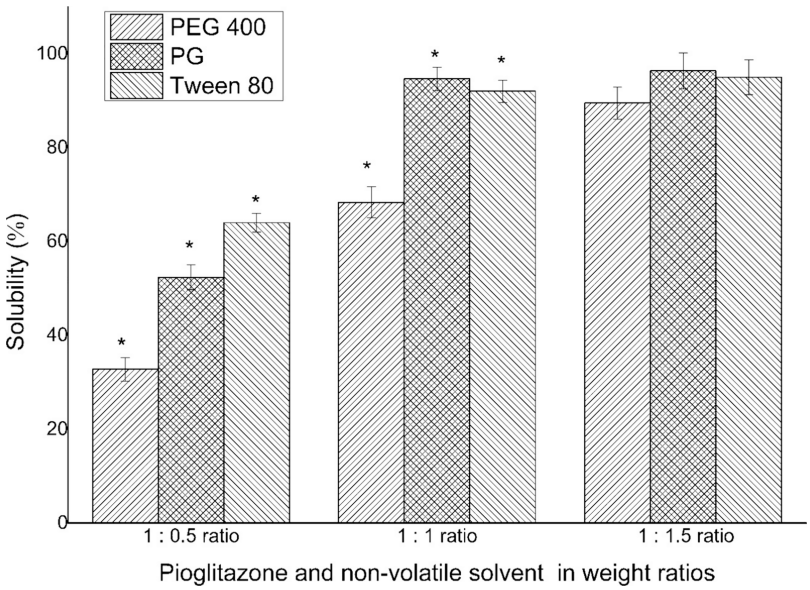


Figure 1. Solubility of developed binary systems (BS1−BS9) using PEG 400, PG, and Tween 80 at different weight ratios (mean ± SD, n = 3; * = 0. 05 level of significance).

Table 4. Precompression Parameter of the Liquisolid Powders[a]

formulation code	angle of repose (deg)	bulk density (g/cm^3)	tapped density (g/cm^3)	CI (%)	HR
LST1	19.13 ± 0.12	0.2457 ± 0.01	0.41 ± 0.83	40.53	0.59
LST2	17.74 ± 0.17	0.2525 ± 0.04	0.34 ± 0.63	26.66	0.73
LST3	21.80 ± 0.18	0.29 ± 0.03	0.43 ± 0.93	32.87	0.67
LST4	23.60 ± 1.10	0.39 ± 0.76	0.42 ± 1.30	25.75	1.64
LST5	17.58 ± 1.20	0.23 ± 0.97	0.37 ± 0.29	37.95	0.62
LST6	20.65 ± 0.94	0.38 ± 0.18	0.51 ± 0.47	25.08	0.74
LST7	20.55 ± 0.47	0.36 ± 1.69	0.38 ± 1.39	34.92	0.95
LST8	17.22 ± 1.44	0.29 ± 1.78	0.48 ± 0.73	38.43	0.61
LST9	19.44 ± 0.21	0.26 ± 0.99	0.36 ± 0.38	28.43	0.71
LST10	17.53 ± 1.59	0.28 ± 1.11	0.52 ± 1.93	44.44	0.55
LST11	19.49 ± 0.53	0.33 ± 1.23	0.37 ± 0.32	22.32	1.11
LST12	22.29 ± 0.87	0.34 ± 1.34	0.39 ± 0.82	31.76	0.88

[a]Values are expressed as means ± SD, n = 3.

($p < 0.05$) in the solubility. On the other hand, PG-containing (BS5 and BS6) and Tween 80-containing (BS8 and BS9) binary formulations showed >95% solubility. Binary formulations using PG and Tween 80 at 1:1 and 1:1.5 weight ratios showed a significant difference ($p < 0.05$) in solubility than their 1:0.5 weight ratio. Formulations prepared (PG and Tween 80) at 1:1 and 1:1.5 weight ratios showed similar pioglitazone solubility ($p > 0.05$). The higher solubility ($p < 0.05$) in the minimum nonvolatile solvents (BS5 and BS8) preferred to formulate the liquisolid tablets. The hydrophilic properties of Tween 80 and PG might contribute to wetting of drug molecules, thereby increasing the solubility.[34] Therefore, BS5 and BS8, which consisted of PG and Tween 80, respectively, were chosen for the liquisolid tablet preparation.

3.4. Formulation of Liquisolid Tablets. The carrier and coating material were used in the process of converting the liquid form of a drug to a powder form. L_f and R were calculated as follows.

$$L_f = \frac{W}{Q} = \frac{30}{150} = 0.2 \tag{6}$$

$$Q = \frac{W}{L_f} = \frac{30}{0.2} = 150 \text{ mg} \tag{7}$$

$$R = \frac{Q}{q} = \frac{150}{7.5} = 20 \tag{8}$$

The increment in the R value resulted in the decrease in the amount of the coating material and enhancement in the amount of the carrier. The quantity of the coating material was estimated from the equation

$$q = \frac{Q}{R} = \frac{150}{20} = 7.5 \text{ mg} \tag{9}$$

From the above calculations, the concentrations of the carrier and coating materials were 150 and 7.5 mg, respectively.

3.4.1. Precompression Parameters. The precompression parameters of the formulations are shown in Table 4. All the formulations exhibited excellent flow properties as the angle of repose value was less than 25°. The bulk and tapped density had shown good density values, which indicated good filling of the die cavity and compression of the tablets. This in particular could affect the thickness and hardness of the tablet. The CI

https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697

Table 5. Postcompression Parameters of the Prepared Liquisolid Tablets

formulation	hardness[a] (kg/cm^2)	average weight[b] (mg)	friability[c] (%)	drug content[d] (%)	disintegration time[e] (min)
LST1	4.22 ± 0.92	187.05 ± 1.43	0.62 ± 0.022	85.31 ± 0.84	5.66 ± 0.25
LST2	3.33 ± 0.24	187.85 ± 0.34	0.72 ± 0.069	93.66 ± 2.75	4.66 ± 0.84
LST3	5.33 ± 0.75	189.00 ± 1.47	0.89 ± 0.034	94.22 ± 0.95	5.00 ± 0.76
LST4	4.66 ± 0.64	187.1 ± 2.39	0.52 ± 0.08	91.30 ± 1.58	5.3 ± 0.18
LST5	5.00 ± 0.95	187.45 ± 1.42	0.19 ± 0.05	87.45 ± 2.65	6.33 ± 1.38
LST6	4.33 ± 0.43	188.4 ± 0.92	0.09 ± 0.03	93.45 ± 1.68	4.00 ± 0.09
LST7	5.33 ± 0.58	190.3 ± 1.94	0.46 ± 0.09	105.34 ± 0.95	5.33 ± 0.19
LST8	4.66 ± 0.42	187.85 ± 2.53	0.76 ± 0.03	89.36 ± 0.91	4.55 ± 0.75
LST9	4.33 ± 0.37	188.4 ± 1.58	0.59 ± 0.04	97.83 ± 1.48	5.33 ± 0.26
LST10	5.13 ± 0.19	187.05 ± 0.42	0.09 ± 0.07	103.91 ± 1.48	2.33 ± 0.83
LST11	5.66 ± 0.33	187.90 ± 2.53	0.08 ± 0.34	86.54 ± 2.47	4.00 ± 0.26
LST12	5.33 ± 0.23	188.65 ± 1.40	0.47 ± 0.91	95.67 ± 0.37	5.00 ± 0.19

[a]Mean ± SD, n = 5. [b]Average ± % deviation, n = 20. [c]Mean ± % deviation, n = 6.5 g. [d]Mean ± % deviation, n = 10. [e]Mean ± SD, n = 6.

and HR values indicated all of the formulations had a good flow property because they were within the prescribed range.[24]

3.4.2. Postcompression Parameters of Liquisolid Tablets. *3.4.2.1. Hardness.* The tablet produced should be hard enough and would not break during transportation, but they should also be soft enough to properly disintegrate following oral administration.[25,26] All the liquid formulations showed acceptable hardness ranging from 3.33 ± 0.24 to 5.66 ± 0.19 kg/cm^2 (Table 5). The physical strength of the tablets prepared by the liquisolid process was further improved when a liquid drug was introduced into the tablet form.

3.4.2.2. Friability. Developed liquisolid tablets had passed the friability test and showed friability in the range of 0.08 ± 0.34 to 0.89 ± 0.03 (Table 5), and there was no tablet that showed cracking, splitting, or broken pieces.

3.4.2.3. Weight Variation. The minimal weight fluctuations were proof that the material had flown evenly during the compression process. The developed liquisolid tablets showed no significant weight variation and remained within the parameters of the IP. The weight variation of all liquisolid tablets ranged from 187.05 ± 1.43 to 190.3 ± 1.94 mg (Table 5).

3.4.2.4. Drug Content. All formulations had drug contents that ranged from 85.31 ± 0.84 to 105.34 ± 0.95 (Table 5), and these values were within the IP limits of 85−115% (Indian Pharmacopoeia, 2018). The absence of significant variation in the drug content indicated that the active ingredient was mixed well with the other excipients in the formulation.

3.4.2.5. In Vitro Disintegration Time. The average disintegration time of each of the formulated liquid tablets was within an acceptable range. Liquisolid formulations from LST1 to LST3 and LST7 to LST9 that were prepared using SSG showed disintegration times ranging from 4.55 ± 0.75 to 5.66 ± 0.25 min (Table 5). Meanwhile, the formulations from LST4 to LST6 and LST10 to LST12 showed disintegration times ranging from 2.33 ± 0.83 to 6.33 ± 1.38 (Table 5). Lower disintegration times of the LST10 batch of tablets indicated rapid drug release. This might be due to the disintegrant crospovidone acting by wicking due to its porous nature. Furthermore, the secondary swelling and rupture of the interparticulate bonds had lowered the disintegration time.[35]

3.4.2.6. Pioglitazone HCl Liquisolid Tablet Dissolution In Vitro Studies. Figure 2 is an illustration of the dissolution profiles of LST1−LST12 formulations. Compared to the pure drug, all liquid formulations showed higher drug release (Figure 6). The liquisolid formulations LST2−LST6 and

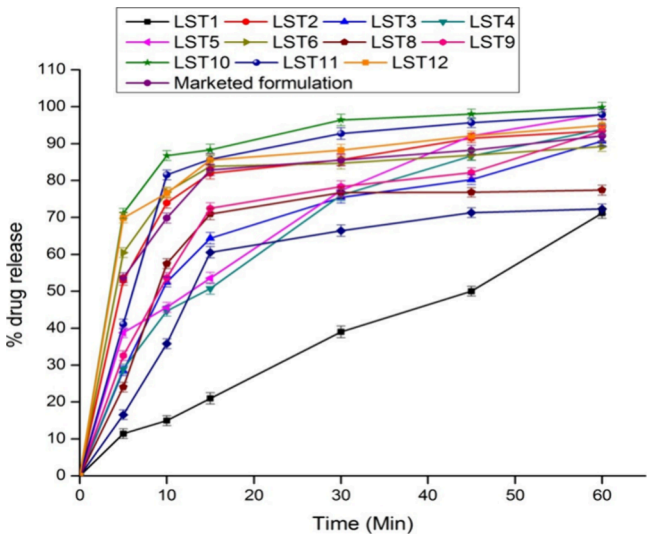


Figure 2. *In vitro* drug release profile of the developed liquisolid tablets (LST1−LST12) (mean ± SD, n = 3).

LST9−LST12 showed more than 85% drug release within 60 min (p < 0.05). LST1, LST7, and LST8 liquisolid tablets resulted in an incomplete drug release within a time period of 60 min (Figure 6). Compared to all formulations, LST10 resulted in completed and highest drug release (p < 0.05). This could be due to the ability of the nonvolatile solvent to decrease the interfacial tension between pioglitazone and the dissolution medium and bridge them. Therefore, the drug was easily diffused from the dissolving surface. Hence, more drugs were diffused in a stagnant diffusion layer and increased the concentration gradient, resulting in better dissolution.[17] The amorphous nature of the binary mixture also contributed to elevating the dissolution of the drug. Wicking and swelling behavior of the disintegrant crospovidone played a major role for quick disintegration into small particles and promoted the dissolution.[35]

3.4.2.7. Dissolution Data Treatment. Q_{15} for the pure drug, LST10, and marketed formulation were 5.65, 88.32, and 82.3%, respectively. The IDR of the LST10 (5.88%/min) was more than that of the marketed formulation (5.48%/min) and pure drug (0.37%/min). The RDR of LST10 was found to be 15.66, which was more than that of the marketed formulation (14.59). The DE of the LST10 had significantly (p < 0.05) improved from 14.48% (pure drug) to 88.77%, and it was 6.31-

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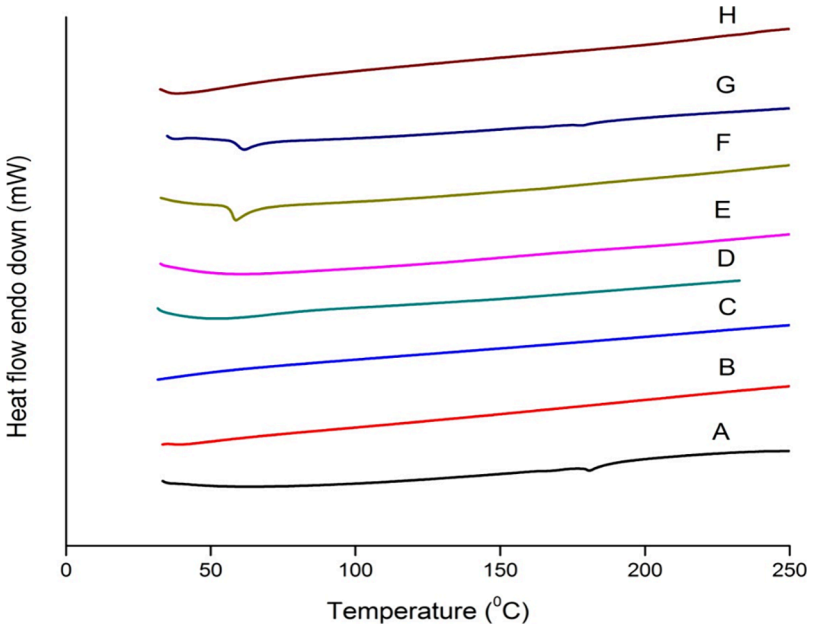

Figure 3. DSC thermograms of (A) pure drug pioglitazone HCl, coating material (B) colloidal silicon dioxide, carrier material (C) MCC, superdisintegrants (D) crospovidone and (E) SSG, binary mixtures (F) BS5 (pioglitazone HCl:PG, 1:1) and (G) BS8 (pioglitazone HCl:Tween 80, 1:1), and (H) optimized liquisolid formulation (LST10).

fold more. The marketed formulation showed 84% DE, which was less than the prepared formulation. The MDT of the pure drug (30 min) was more than that of the LST10 (5.80 min) and marketed formulation (9.59 min). However, the optimized formulation (LST10) showed less MDT. It signified better enhancement of solubility of pioglitazone in a minimum time. The increased dissolution rate of the drug pioglitazone could possibly be due to the liquisolid compact form. In addition, the values of the difference factor (f_1) and similarity factor (f_2) between LST10 and the marketed formulation were found to be 8.78 and 51.92, respectively. As the values were less than 15 and more than 50, it signified a similarity between LST10 and the marketed drug.[27] The *t* test was applied between LST10 and the marketed formulation. The calculated *t* value was found to be 2.31, and the critical value was 2.01. The statistical study showed a rejection of the null hypothesis in the *t* test, as the estimated *t* value was significantly higher than the tabulated *t* value of the dissolution data of the formulation. This showed a statistically significant difference in the dissolution profiles at $p < 0.05$. Thus, the findings of the study confirmed that the liquisolid technique played an important role in improving the solubility and dissolution rate of pioglitazone.

3.4.3. FTIR. Figure S2A,C displays the FTIR spectra of pioglitazone HCl, excipients, binary mixtures, and the optimized liquisolid tablet. Individual characteristics of the absorption peaks were observed in the FTIR spectra of the pure drug pioglitazone HCl, indicating the presence of various functional groups. The peaks at 3354.67, 3084.18, 2927.94, and 1680 cm^{-1} in the FTIR spectra confirmed the presence of N−H stretching, C−H aromatic, C−H aliphatic stretching, and C═C stretching, respectively. Furthermore, the C═O stretching vibration showed the characteristic peaks at 1741.72 and 1680 cm^{-1} (Figure S2A). Both Chowdary et al.[28] and Suryadevara et al.[29] came to similar conclusions in their studies. This further attested to the confirmation of the identity of the pure drug pioglitazone HCl. There were no new peaks in the binary mixtures (Figure S2I,J), thus signifying the compatibility with solvents.[27] On the other hand, the microcrystalline cellulose showed O−H stretch (3328.5 cm^{-1}) and alkane C−H stretch (2894.3 cm^{-1}) (Figure S2E). The characteristics peak at 1085 cm^{-1} (stretching) illustrated the silicon dioxide (Figure S2F). The FTIR spectra of LST10 (Figure S2K) exhibited identical peaks of the drug and excipients, and there was no major shift in the peak values. These findings indicated the chemical compatibility between pioglitazone and the excipients.

3.4.4. DSC. Figure 3 indicates the DSC thermograms of pioglitazone HCl, excipients, binary mixtures, and the optimized liquisolid formulation. A single sharp endothermic peak was observed at 180.88 °C for the pure drug pioglitazone HCl (Figure 3A), which represented its melting point. In addition, the drug had an enthalpy of fusion (ΔH) of 33.67 J/g, a measure used to determine the crystallinity of a substance (Bonthagarala et al.[14] and Swain and Subudhi[21]). This confirmed the crystalline properties of the pure drug. Figure 3B−E shows no peaks, which indicated the amorphous nature of the excipients. The endothermic peak representing the melting of the solvent was observed in the thermogram of the binary mixtures, along with a smaller, broader endothermic peak with a lower intensity, and expressed the melting of the pioglitazone HCl at 178.57 °C with the heat capacity of 6.71 J/g (Figure 3F,G). This implied the transformation of the drug into an amorphous state. In the DSC thermogram of the optimized liquid solid formulation LST10 (Figure 3H), there was no melting peak observed in the drug or the excipients. The fact that the characteristic peak had disappeared was more than enough proof needed to confirm the presence of pioglitazone in the system as a solution. Naureen et al. reported similar results while studying the mirtazapine liquisolid compact using propylene glycol as a solvent.[22] It is possible that these findings will contribute to an increase in the solubility of the drug and its ability to dissolve. The absence of a new sharp peak suggests that the drug and excipients are

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ACS Omega 2024, 9, 42687−42697

compatible with each other. This confirms the stability and robustness of the developed formulation.[31,32]

3.4.5. XRD. Figure 4 demonstrates the XRD peak of pioglitazone HCl and the formulations. Pioglitazone HCl showed the distinctive diffraction peaks at 2θ° corresponding to 6.85, 10.35, 13.80, 16.99, 17.83, 18.95, 24.21, 25.42, and 31.30°, which were extremely sharp and intense (Figure 4A). These peaks provided substantial evidence that pioglitazone hydrochloride was in the crystalline form (Swain and Subudhi[21]). The drug peaks in the diffraction patterns of the binary mixtures were weaker (Figure 4B,C). This confirmed that the drug could undergo a transition phase, from the crystalline to amorphous state. In addition, the liquid−solid compact showed that pioglitazone was partially soluble in liquid. It was presumed that the amorphous state of the drug was responsible for the improvement in its solubility as well as its bioavailability.[22,33]

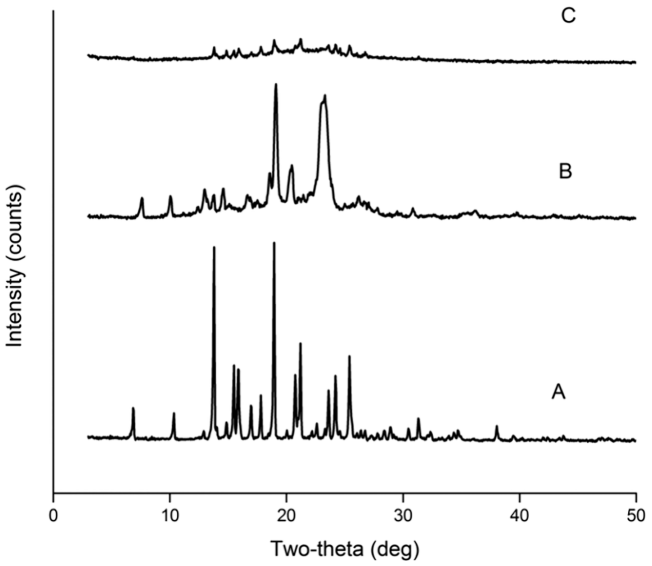

Figure 4. X-ray diffraction patterns of (A) pure drug pioglitazone HCl, binary mixture (B) BS5 (pioglitazone HCl:PG, 1:1), and (C) BS8 (pioglitazone HCl:Tween 80, 1:1).

3.4.6. SEM. Figure 5A illustrates the crystals of pioglitazone HCl with a needle-like structure and variation in size. These results validated the XRD study, which showed that pioglitazone HCl had crystalline properties. The SEM images of the binary mixtures of pioglitazone HCl showed that there were no crystal needles of the drug (Figure 5B,C), indicating that the drug had lost its crystalline property in the liquisolid compact. Furthermore, the results of the DSC and XRD studies were verified by these observations. The photomicrograph in Figure 5D indicated that the binary mixture was coated with coating materials and formed a liquid formulation suitable for tablet compression.[23]

3.5. Physical Stability Test. LST10 stability was evaluated according to the guidelines of ICH on 0, 1, 2, and 3 months using the dissolution study.[35] The dissolution profiles (Figure 6) of LST10 were similar after 3 months ($p > 0.05$), and the f_2 value (82.47) ensured equivalence of the two profiles (Prajapat et al.[27]). The hardness values of the stored LST10 formulation were 5.16 ± 0.14, 5.14 ± 0.21, and 5.10 ± 0.32 kg/cm^2 after 1, 2, and 3 months, respectively. The disintegration times were 2.58 ± 0.92, 2.46 ± 0.88, abd 2.61 ± 0.73 min at predetermined time periods. There was no significant difference ($p > 0.05$) of the hardness and disintegration time as compared to the initial month. These indicated the stability of the LST10 formulation.

3.6. *In Vivo* Studies. Based on the data presented above, LST10 was chosen as the optimized formulation for an additional investigation. Rabbits were used as an animal model for an *in vivo* study on the bioavailability of pure pioglitazone, HCl, and LST10. Figure 7 illustrates the plasma concentration−time curves after oral administration of pure pioglitazone HCl[8] and LST10. The same has been published previously.[8] The findings of the pharmacokinetic parameters are displayed in Table 6. There was a statistically significant difference when the pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of LST10 were examined at a significance level of 0.05%. In plasma, the T_{max} values of LST10 and the pure drug were found to be similar (Table 6). The findings suggested that the same mechanism was responsible for the absorption of the drug. Compared with pure pioglitazone HCl, the C_{max} of LST10 was considerably ($p < 0.05$) 4.18-fold higher. The rapid release of pioglitazone HCl from the tablet was likely responsible for the observed increase in the level of C_{max}. This explained the better dissolution of the selected tablets. As a result, the bioavailability had increased significantly. As shown in Figure 7, the initial plasma levels (within 0.5 h) of the drug in the LST10 tablet formulation were 6.36-fold higher than the pure drug after oral administration to the rabbits. Compared with the pure drug, the AUC_{0-t} of pioglitazone HCl from the LST10 was ($p < 0.05$) 3.06-fold higher than the pure drug (Table 6). The MRT ($p > 0.05$) and $t_{1/2}$ ($p > 0.05$) were compared with those of the pure drug. The underlying pharmacokinetic parameters provided evidence that the bioavailability had improved. The possible explanation for the significant increase in the bioavailability was the improvement in the dissolution rate.

3.7. IVIVC. IVIVC was used to justify the development of the optimized formulation. Following oral administration, the fraction of pioglitazone released (F_r) was correlated with the fraction of pioglitazone absorbed (F_a). F_r was determined from the dissolution data. The Wagner−Nelson method was used to deconvolve the *in vivo* data and determine F_a over time, as depicted in eq 10.

$$F_a = \left[\left(\frac{C_t + k_e AUC_{0-t}}{k_e AUC_{0-\infty}}\right)\right] \times 100 \quad (10)$$

where C_t is the observed plasma concentrations and k_e is the elimination rate constant.

A plot of F_r against F_a showed a good correlation (r^2 = 0.929) as shown in Figure S3. Considering the point to point correlation observed between F_r and F_a, this can be considered as the level A correlation. Accordingly, the measurement of the *in vitro* dissolution rate alone is sufficient to determine the biopharmaceutical rate of the dosage form. The USFDA considers high permeability and high solubility to be the criteria (BCS-I) for biowaiver studies. Based on the notable enhancement in pioglitazone (BCS-II) solubility and good IVIVC, the biowaiver potential for this formulation can be speculated.

4. CONCLUSIONS

The results of this study show that the liquid−solid technique is an extremely promising method to improve the dissolution

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ACS Omega 2024, 9, 42687−42697

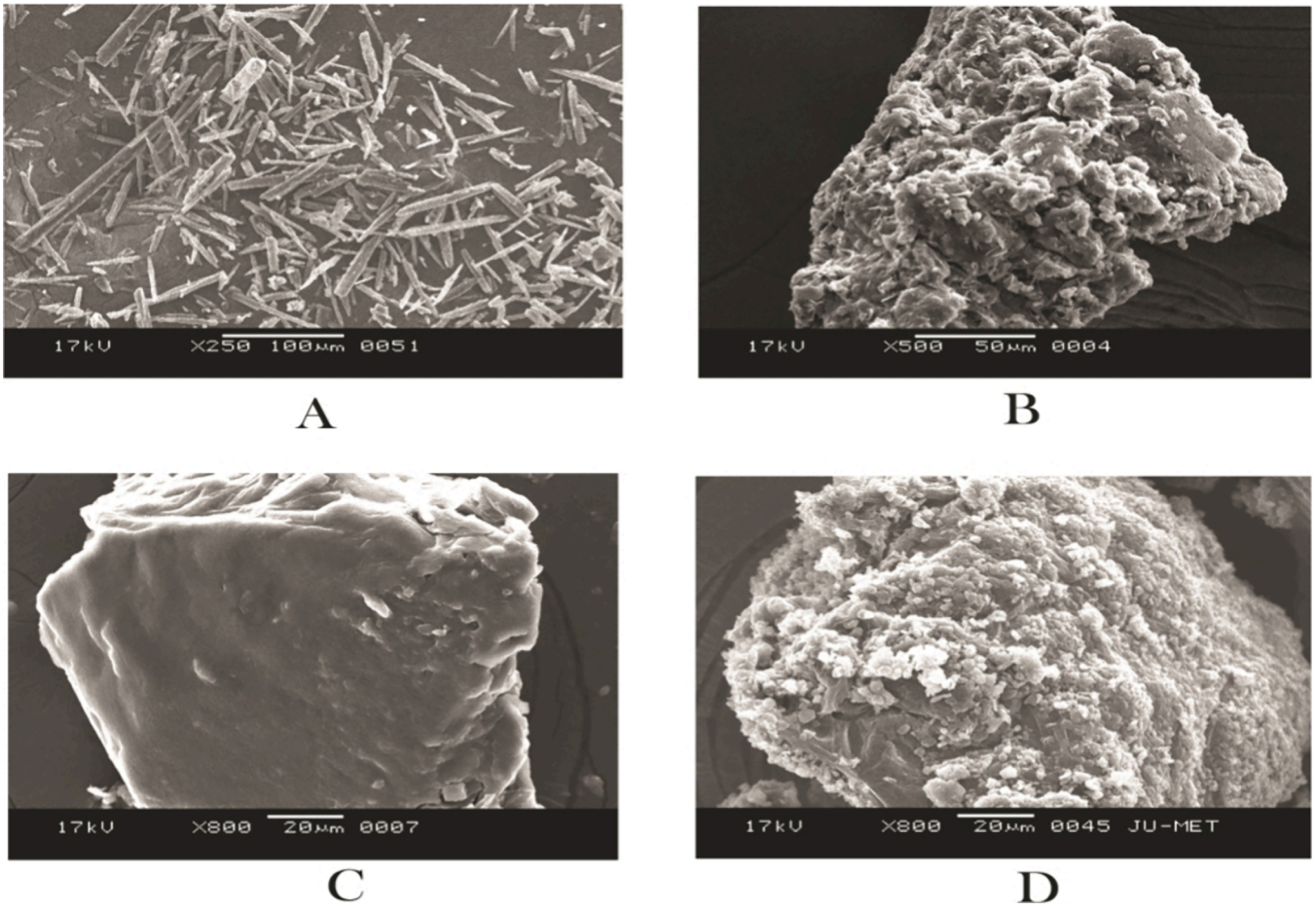

Figure 5. SEM of (A) pure drug pioglitazone HCl (250X), binary mixture (B) BS5 (pioglitazone HCl:PG, 1:1) (500×), (C) BS8 (pioglitazone HCl:Tween 80, 1:1) (800×), and (D) optimized liquisolid formulation (LST10) after application of the carrier and coating materials (800×).

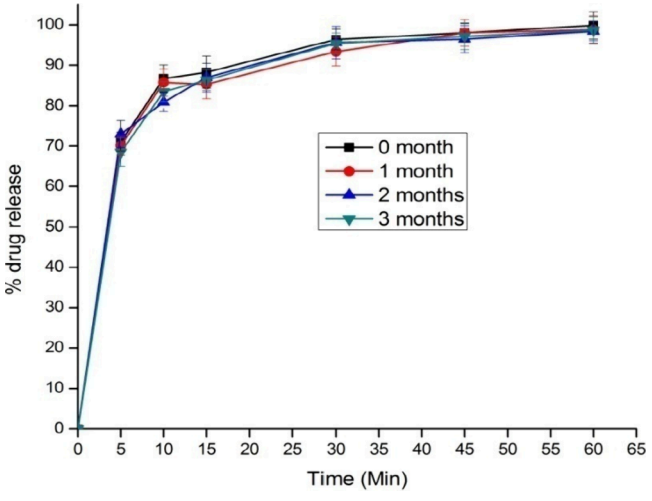

Figure 6. Stability study: dissolution profile of LST10 after 1, 2, and 3 months of storage at accelerated conditions (mean ± SD, n = 3).

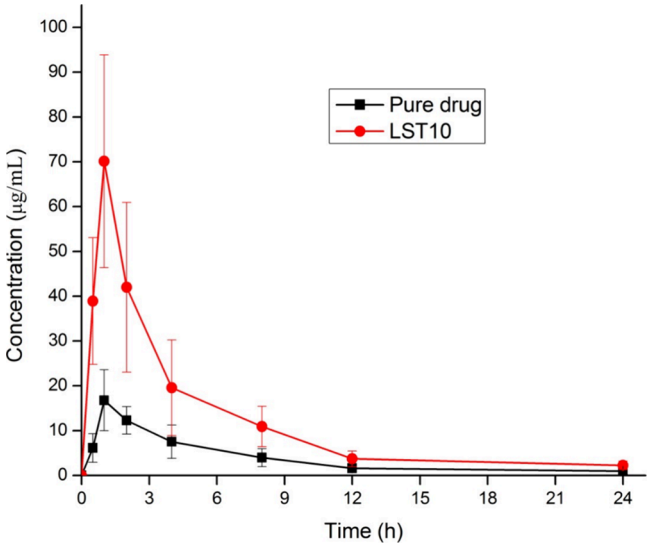

Figure 7. Plasma profiles of the pure drug pioglitazone HCl and the optimized formulation LST10 (mean ± SD, n = 3).

and bioavailability of pioglitazone HCl. FTIR and DSC revealed a compatibility between the optimized excipient and the model drug pioglitazone. The transition from a crystalline to amorphous state was demonstrated by DSC, XRD, and SEM. The selected excipients (Tween 80, MCC, colloidal silicon dioxide, and crospovidone (0.5%)) had resulted in a stable optimized formulation (LST10), and their combination showed promising results as seen in the improvement of the dissolution rate and bioavailability. The developed batches showed acceptable physiochemical properties, disintegration time, and dissolution profile. The stability of the optimized formulation showed no significant changes in the tablet

https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697

Table 6. Pharmacokinetic Parameters of Pure Drug and LST10 in Rabbits (Mean ± SD, n = 3)

parameter	pure drug	LST10
T_{max} (h)	1.00 ± 0.001	1.00 ± 0.001
C_{max} (μg/mL)	16.78 ± 6.81	70.11 ± 12.51
AUC_{0-t} (μg h/mL)	91.52 ± 37.18	280.32 ± 117.68
$AUC_{0-\infty}$ (μg h/mL)	99.54 ± 38.19	295.65 ± 119.88
MRT (h)	8.28 ± 0.87	6.49 ± 0.06
$t_{1/2}$ (h)	5.63 ± 0.35	4.78 ± 0.07

properties at the end of the three-month period. This is an alternative approach to improve bioavailability and develop the most suitable dosage form. This approach can be extended to other poorly water-soluble drugs to achieve optimal therapeutic efficacy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c09145.

(Figure S1) HPLC chromatogram of pioglitazone HCl; (Table S1) estimation of pioglitazone HCl in plasma samples by RP-HPLC; (Figure S2) FTIR spectra of pure drug pioglitazone HCl, nonvolatile solvents PEG 400, PG, and Tween 80, carrier material MCC, coating material colloidal silicon dioxide, super disintegrants SSG and crospovidone, and binary mixtures BS5 (pioglitazone HCl:PG, 1:1), BS8 (pioglitazone HCl:Tween 80, 1:1), and the optimized liquisolid formulation (LST10); (Figure S3) *in vitro*−*in vivo* correlation of the optimized liquisolid formulation (LST10) (PDF)

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Author Contributions

R.P.S. performed conceptualization, methodologies, interpretation, data curation, visualization, supervision, writing of the original draft, and review and editing of the manuscript; G.O.E. performed validation, data curation, visualization, writing of the original draft, supervision, and review and editing of the manuscript; A.B. performed methodologies, formal analysis, interpretation, data curation, visualization, writing of the original draft, and review and editing of the manuscript; R.K.S. and J.K. performed interpretation, data curation, visualization, writing of the original draft, and review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to thank the Chalapathi Institute of Pharmaceutical Sciences, Andhra Pradesh for providing the animal facilities and the School of Pharmaceutical Sciences, Siksha O Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India, for providing lab facilities for the completion of this project.

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https://doi.org/10.1021/acsomega.3c09145
ACS Omega 2024, 9, 42687−42697