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ENHANCEMENT OF PIOGLITAZONE HYDROCHLORIDE SOLUBILITY THROUGH LIQUISOLID COMPACT FORMULATION USING NOVEL CARRIER NEUSILIN US2

Bhushan Rajendra Rane[1*], Dnyaneshwar Sopan Gaikwad[1], Ashish Suresh Jain[2], Prashant Lakshaman Pingale[3], Nayan Ashok Gujarathi[4]

1. ***Department of Pharmaceutics, Shri D. D. Vispute College of Pharmacy & Research Centre, Panvel-410221, India.***
2. ***Department of Pharmacognosy, Shri D. D. Vispute College of Pharmacy & Research Centre, Panvel-410221, India.***
3. ***Department of Pharmaceutics, GES's Sir Dr. M. S. Gosavi College of Pharmaceutical Education and Research, Nashik-422005, India.***
4. ***Department of Pharmaceutics, SVKM's Institute of Pharmacy, Dhule-424001, India.***

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ABSTRACT

Main objective behind formulating any dosage form is to develop the optimized and stable dosage from which will releae the drug fastly in conventional formulations. Various approaches such as, solid dispersion, crystal engineering, ball milling, complexation, and self-emulsifying drug delivery systems have all been used in recent research to increase the solubility of the drug, but the liquisolid compact has demonstrated superior results for enhancing dissolution. In most of the cases absorption of drug is less which is due to various factors one of the most important factor is drug solubility. Liquisolid compacts are a novel and promising addition to such a novel goal because the liquisolid technology has been successfully used to treat low-dose poorly soluble drugs. A thiazolidinedione, pioglitazone HCl is primarily prescribed to type 2 diabetics as an anti-hyperglycemic medication. Compared to traditional carrier materials, Neusilin US2 performs better as a carrier material in liquisolid compact. Drugs from BCS Class II can be easily formulated using liquisolid compact by the simple blending method. A drug having a low dose can be formulated by this method.

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Introduction

The efficacy of the drug depends on the availability of bioavailability depending on the melting of the drug cells. One of the most crucial factors in achieving the desired drug concentration in the distribution system to reflect the drug response is solubility. Drugs with a low solubility in water will ordinarily release at a slower rate due to their low solubility in GI content. The dissolution rate is the process that determines how quickly drugs are absorbed. To speed up the rate of dissolution, drugs that are poorly water soluble are in demand. Contrarily, this enhances bioavailability and absorption. There are ongoing developments in formulation techniques for improving poorly soluble substances' dissolution [1].

Liquisolid compacts are one of the most innovative and promising approaches to encourage the eradication of water-insoluble medications among them. Liquisolid compacts are pills or tablets that release immediately or continuously after being swallowed, along with the addition of any necessary adjuvants for tablets or encapsulating them [2].

With a neutral pH, Neusilin® US2 is a synthetic, amorphous magnesium aluminum oximetasilicate that can be utilized for both wet granulation and direct compression of solid dosage forms [3].

Only if a maximum liquid load on the carrier material is not exceeded can one obtain an acceptable flowing and compressible liquid-solid system depending on the excipient ratio (R) of the powder substrate. The weight ratio of the liquid

Corresponding Author: Bhushan Rajendra Rane; Department of Pharmaceutics, Shri D. D. Vispute College of Pharmacy & Research Centre, Panvel-410221, India. E-mail: rane7dec@gmail.com.

formulation (W) and the carrier material (Q) in the system is known as the "liquid/carrier ratio" or "liquid load factor" (Lf [w/w]) [4]:

$$LF = W/Q \quad (1)$$

R represents the ratio between the weights of the carrier (Q) and the coating (q) material present in the formulation:

$$R = Q/q \quad (2)$$

The liquid load factor that ensures acceptable flowability (L f) can be determined by:

$$Lf = \Phi + \varphi . (1/R) \quad (3)$$

Where Φ and φ are the Φ-values of the carrier and coating material, respectively. Similarly, the liquid load factor for the production of liquisolid systems with acceptable compatibility (ΨLf) can be determined by

$$L_f = \Psi + \psi . (l/R) \quad (4)$$

Where Ψ and ψ are the carrier and coating material, respectively.
Pioglitazone HCl is an antidiabetic drug that is used for the treatment of type 2 diabetes. It is a hydrochloride salt of orally active Thiazolidinedione which are having antidiabetics as well as antineoplastic properties. Their glucose-lowering effect is primarily mediated by improved insulin sensitivity, which makes it easier to absorb and use glucose. Thiazolidinedione can go into the nucleus and bind to PPARγ [5].

The Rationale behindthe Selection of Liquisolid Compact

- The primary objective of the liquisolid compact system is to improve the solubility of the poorly aqueous soluble drug.
- It also improves the photostability of the drug in the solid dosage form.
- The drug is dispersed at the molecular level in the formulation.
- It also minimizes the effect of pH variation on drug release.
- The sustain release formulation can be formulated by using different hydrophobic carriers.
- The production of the tablet is the same as that of a conventional tablet.
- Provide a large surface area available for absorption.

By simply blending the liquid medication with specific powder excipients known as the carrier (cellulose, starch, lactose, etc.) and coating (silica) materials, the liquid medication can be transformed into a dry-looking, nonadherent, free-flowing, and easily compressible powder [6, 7].

Materials and Methods

Preformulation Studies
Organoleptic properties: The pure drug's color and appearance were checked by visual inspection and the observation is noted [8].

Physicochemical Properties
Determination of Solubility
A solubility study of Pioglitazone HCl is performed to confirm its purity by saturation method and measurement using UV-Vis double beam spectrophotometer [9].

Melting Point Determination
Using Thiele's tube method, the melting point of pioglitazone HCl was ascertained. The drug was inserted into the glass capillary, which had been sealed at one end. The capillary was then inserted into a Thiele's tube filled with liquid paraffin. The tube was heated and the melting of drug particles at a certain temperature was observed. The temperature was noted down when the particles just started to melt and after removing the burner noted the temperature at which the reappearance of solid structure (Flashpoint) [10].

Estimation of λ Max and Plot of Calibration Curve by UV-Visible Spectrophotometer
Preparation of Standard Calibration Curve of Pioglitazone HCl in 0.1N HCl
Preparation of working standard stock solution: Drug weighed and dissolved in 0.1N HCl to obtain a concentration of 100 ppm. This solution was used as a standard stock solution to obtain further dilutions.

Spectrophotometric scanning of Pioglitazone HCl

From the stock solution the dilution was prepared at10 ppm and the UVscan was performed between the wavelength range of 200-400 nm and the highest peak in the spectra was selected as the maximum wavelength for Pioglitazone HCl.

The standard plot of pioglitazone HCl in 0.1 N HCl was created by preparing dilutions of 2, 4, 6, 8, and 10 ppm from the standard stock solution and measuring the absorbance with a UV-Vis double beam spectrophotometer [11].

FTIR Studies

Confirmation of drug and its purity by FTIR: The FTIR spectra of Pioglitazone HCl wererecorded using Shimadzu IR Affinity-IS. The drug sample was placed in an FTIR sample holder and scanned over the range of 500 to 4000 cm-1. The spectrum was confirmed by comparing it with the IR spectra of Pioglitazone HCl [12].

A drug-excipients Study by FTIR

The IR spectrum of API, excipients, and drug-excipients mixture were recorded by FTIR. The compatibility of the drug and excipients was checked by comparing different spectrums obtained from FTIR studies [13].

The composition of various batches of liquisolid compact Pioglitazone HCl is shown in **Table 1**.

Table 1. Composition of various batches of liquisolid compact of Pioglitazone HCl

Batch code	Drug Conc. in vehicle (%)	R = Q/q	Wt. of the drug in sol.(gm)	Loading Factor	Neusilin US2 (mg)	Aerosil 200 (mg)	Croscarmellose %	Weight of Tablet (mg)
F1	50	30	0.015	1.270	39.37	1.31	4(2.82)	73.50
F2	50	40	0.015	1.242	40.26	1.00	3(2.13)	73.39
F3	50	50	0.015	1.226	40.80	0.82	2(1.43)	73.05
F4	60	30	0.02	1.270	47.24	1.57	4(3.31)	86.18
F5	60	40	0.02	1.242	48.30	1.20	3(2.47)	84.97
F6	60	50	0.02	1.226	48.94	0.97	2(1.65)	84.56
F7	70	30	0.025	1.270	55.11	1.84	4(3.71)	96.66
F8	70	40	0.025	1.242	56.36	1.41	3(2.81)	96.58
F9	70	50	0.025	1.226	57.10	1.14	2(1.88)	96.12

Pre-compression Evaluation Study

Bulk Density

Without moving the cylinder, the powder's volume was measured, and the equation was used to calculate the bulk density,

$$\text{Bulk density (BD)} = \frac{\text{Weight of powder}}{\text{Bulk volume}} \quad (5)$$

Tapped Density

Accurately weighed quantities of a sample of powder were placed in a 25ml measuring cylinder. Standard procedure was followed to determine tapped density by using Digital Bulk Density Apparatus [14]. The final volume was noted and tap density was calculated using the equation

$$\text{Tapped density (TD)} = \frac{\text{Weight of powder}}{\text{Tapped volume}} \quad (6)$$

Carr's Index

Carr's index is frequently used as flowability characteristics. Carr's index of 5-15% is considered excellent and acceptable upto 21%, while the index greater than 23% indicates poor flow. It is calculated by using the formula,

$$\text{Carr'sindex (I)} = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100 \quad (7)$$

Hausner's Ratio

Hausner's ratio is an indication of the flow ability of powder. Hausner's ratio of less than 1.25 indicates good flow [15]. It is calculated by the formula,

$$\text{Hausner's ratio} = \frac{\text{TD}}{\text{BD}} \quad (8)$$

The Angle of Repose

The powder's flowability can be determined by looking at the Angle of repose. The lower portion of the funnel was held 2 cm away from the table's surface. The funnel released 9.5gm of powder, which was then poured into a pile. The funnel was then raised to the pile's height and a circle was drawn around it. The pile height (h) was used to determine how high the tip was above the table's surface, and the pile diameter (d) was determined by averaging three different circle diameters [15]. An equation was used to calculate the angle of repose,

$$Tan\ \theta = \frac{h}{r} \ldots . \text{EqnNo. } 9 \quad (9)$$

Solubility Study of Liquisolid Compact

The absorbance was determined using a UV-Vis double beam spectrophotometer after the powder was dissolved in water until a supersaturated solution was created [16].

The bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose are the pre-compression parameters listed in **Table 2**.

Table 2. Pre-compression evaluation of liquisolid compact of Pioglitazone HCl

Batch Code	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Hausner's Ratio	Parts of solvent per part of solute
F1	0.52 ±0.005	0.569±0.001	28.89±0.617	8.61±0.04	1.094±0.0051	1145.47
F2	0.49 ±0.01	0.592±0.0028	32.45±1.316	17.22±0.092	1.208±0.001	1562.5
F3	0.484 ±0.01	0.525 ±0.035	26.39±1.460	7.81±0.051	1.084±0.0028	969.93
F4	0.55 ±0.002	0.685 ±0.056	30.18±0.594	19.70±0.132	1.245±0.014	1430.61
F5	0.483±0.001	0.532 ±0.031	34.28±0.623	9.21±0.0017	1.101±0.023	1256.28
F6	0.574±0.003	0.637 ±0.028	29.32±0.357	9.89±0.11	1.109±0.028	1215.06
F7	0.516 ±003	0.563 ±0.013	27.65±2.193	8.35±0.005	1.091±0.040	999.00
F8	0.5 ±0.005	0.541 ±0.026	33.11±0.484	7.54±0.028	1.082±0.0057	1086.95
F9	0.52 ±0.005	0.635 ±0.027	31.43±0.392	18.11±0.051	1.221±0.0075	1112.35

Note: Solubility of the drug is determined by parts of solvent required per part of solute and that is 3558.71. The solubility of the drug is increased in these 9 formulations and that is noted in the above table.

Preparation of Tablet

Pioglitazone HCl was precisely weighed and then combined with the liquid vehicle, PEG 400, to create the drug suspension. Neusilin US2 and Aerosil 200 were added to the aforementioned suspension as a carrier and coating material, respectively. Croscarmellose was added as a super disintegrant to the prepared liquid-solid system before the mixture was combined and compressed into a tablet using a 6 mm punch on the Kambert multi-station tablet compression machine [17].

Post Compression Evaluation Study

Weight Variation

The average weight of 10 tablets was determined after they were weighed. Following that, each tablet was weighed separately. Calculations were made to determine each tablet's percentage weight deviation from the average weight [18].

Friability

The Digital Programmable Friability Apparatus was used to gauge the tablet's friability. 4 tablets were transferred to the friability after being weighed (W initial). For 4 minutes, the friabilator was run at 25 rpm. The tablets were once more weighed (W final). Then, the percentage of friability was determined [18].

Hardness

The Monsanto hardness tester was used to gauge the tablet's hardness. It is stated as kg/cm^2 [18].

Thickness

By using a screw gauge, the tablets' diameter and thickness were calculated and expressed in millimeters [17].

Percent Drug Release

Using the USP type II (paddle) dissolution testing apparatus, the percent drug release over a period of one was calculated (LABINDIA). 900 ml of 0.1 N HCl were used as the dissolution medium, which was agitated at 50 rpm and 37.5°C. To estimate the release of pioglitazone HCl, 5 ml samples were taken at 0, 5, 10, 15, 20, 25, 30, 35, 40, 45, and 60 minutes. At each time interval, the same amount of the dissolution medium was replaced. Pioglitazone HCl was determined in the samples using a UV spectrophotometer at 221 nm for 0.1 N HCl [19].

Percent Drug Content

Twenty tablets were taken and ground into a powder using a mortar and pestle to calculate the percent drug content. 10 mg of the drug's equivalence in powder form was taken, and the proper amount of solvent was used to dissolve it. The amount of drug within the tablet was analyzed after proper dilution of the test solution by using a UV spectrophotometer against the reference solution with suitable dilutions at 227nm for ethanol [20].

Stability Study

The stability studies are under process and are carried out as per ICH guidelines [21, 22].

Several post-compression parameters are shown in **Table 3**, including weight variation, friability, hardness, thickness, percentage drug release, and percentage drug content.

Table 3. Post Compression evaluation of liquisolid compact of Pioglitazone HCl

Batch code	The average weight of the tablet	Hardness (kg\cm^2)	Thickness (mm)	Friability	Disintegration time (seconds)	Drug Content (%)
F1	73.82±0.352	2±0.346	2.44±0.034	0.235	14±0.69	93.80±0.404
F2	73.12±0.213	3±0.404	2.42±0.017	0.240	18±0.17	96.53±0.421
F3	74.06±0.080	2±0.173	2.48±0.0173	0.118	25±1.55	101.97±1.310
F4	86.23±0.063	2±0.173	2.46±0.028	0.117	22±1.90	97.21±0.236
F5	84.77±0.294	3±0.230	2.40±0.011	0.353	15±1.50	99.25±0.663
F6	84.45±0.011	2±0.173	2.39±0.0173	0.468	20±0.92	96.53±0.964
F7	96.79±0.046	2±0.12	2.51±0.005	0.234	19±1.32	99.93±0.271
F8	96.65±0.115	3±0.230	2.43±0.017	0.352	22±1.32	100.61±0.640
F9	96.49±0.167	2±0.173	2.45±0.046	0.354	28±0.80	96.53±0.329

Results and Discussion

Estimation of λ Max and Plot of Calibration Curve by UV-visible Spectrophotometer

Pioglitazone HCl in Ethanol Spectrophotometric Scanning: The precisely weighed medication was dissolved in ethanol to achieve a concentration of 100 ppm. To obtain additional dilutions, this solution served as a standard stock solution. From the stock solution, the dilution was prepared at10 ppm and the UV scan was performed between the wavelength ranges of 200-400 nm. The maximum wavelength for Pioglitazone HCl in ethanol was found to be 227nm.

Spectrophotometric Scanning of Pioglitazone HCl in 0.1N HCl

The drug was precisely weighed and dissolved in 0.1N HCl to produce a 100 ppm concentration. This solution was used as a standard stock solution to obtain further dilutions. From the stock solution, the dilution was prepared at10 ppm and the UVscan was performed between the wavelength ranges of 200-400 nm. The maximum wavelength for Pioglitazone HCl in 0.1N HCl was found to be 227 nm. UV- Visible absorption spectra of Pioglitazone HCl in 0.1N HCl is shown in **Figure 1**.

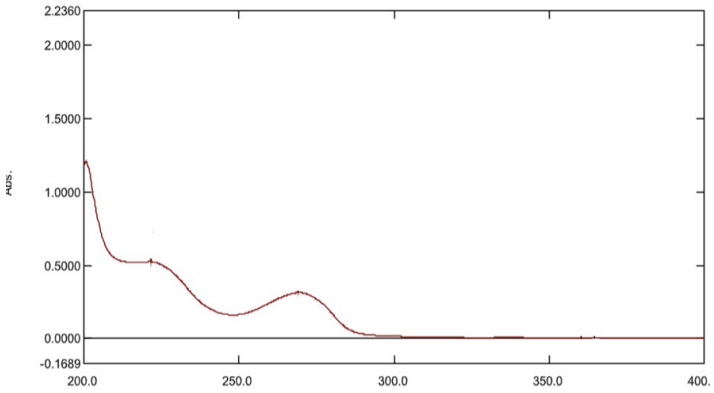

Figure 1. UV- Visible absorption spectra of Pioglitazone HCl in 0.1N HCl

Calibration Curve and Linearity of Pioglitazone HCl in 0.1N HCl

Dilutions of 2, 4, 6, 8, and 10 ppm were made from the standard stock solution, and the absorbance was assessed using a UV-Vis double beam spectrophotometer. **Figure 2** displays a calibration curve and the linearity of pioglitazone HCl in 0.1N HCl.

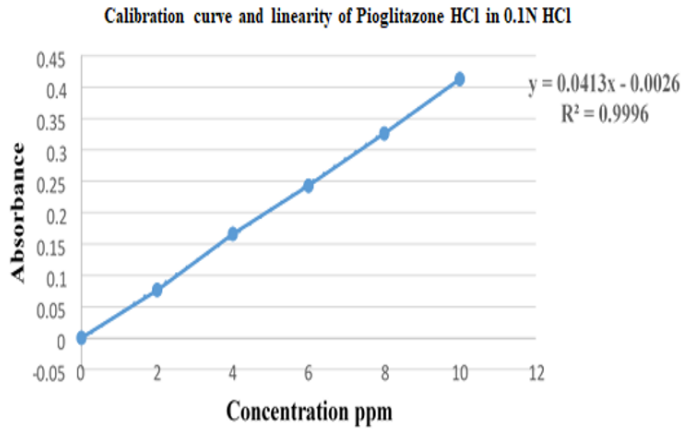

Figure 2. Calibration curve and linearity of Pioglitazone HCl in 0.1N HCl

Dissolution Study

In vitro dissolution tests were performed using the USP type II method and a phosphate buffer pH 7.4 medium. Every 5 minutes, samples were taken, and the UV spectrophotometer measured the absorbance at 234 nm. **Figure 3** depicts the cumulative% drug release for batches F1 to F9 of the formulation of Pioglitazone HCl liquisolid compact.

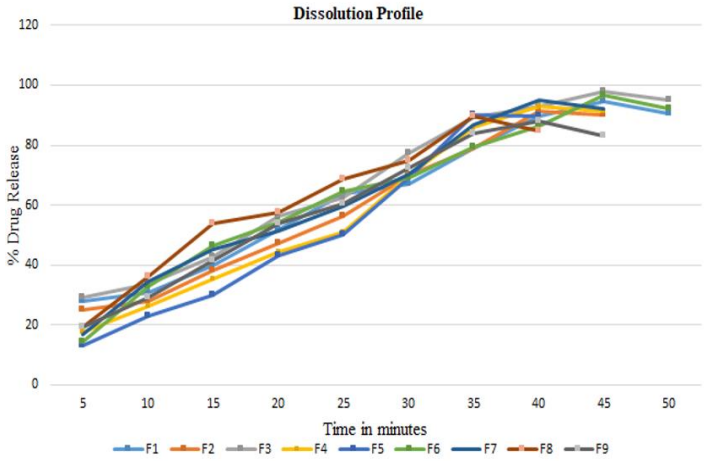

Figure 3. Cumulative % drug release for the formulation ofliqui-solid compact of Pioglitazone HCl (BatchF1-F9)

Powder x-ray Diffraction Studies

Drug polymorphisms are a significant factor that may influence the rate of drug dissolution and, consequently, bioavailability. The polymorphic alterations of pure drugs in liquisolid systems must therefore be studied. The distinctive PXRD pattern, which displayed strong peaks at 18°, 20°, 28°, and 30° locations, was used to study the drug's crystalline composition. The lack of these recognizable drug peaks in the x-ray diffraction pattern of the liquisolid powder indicated that the pure drug had completely changed into an amorphous or solubilized form. The drug's solubilization in a liquid vehicle, which may be absorbed and adsorbed on the carrier and coating, may be the cause of the liquid-solid formulation's lack of crystallinity.

Stability Study

The physical-chemical properties and dissolution of liquisolid tablets were examined in the stability tests to see how storage at 40° C, 2°C, and 75 percent, 5 percent RH affected them. The best formula from three batches is stored for three months at 40° (C ±2°C) and 75% (±5%RH). In terms of their physical traits, hardness, thickness, drug content, or dissolving test, the aged liquisolid tablets and the fresh ones did not exhibit any discernible differences. This proves the liquisolid pills were stable during storage under these conditions. **Table 4** shows the findings of the stability study conducted over three months for various parameters, including appearance, hardness, average weight, drug content, and disintegration time.

Table 4. Stability study of optimized formulation of liquisolid compact of Pioglitazone HCl

Sr. No	Parameters	Time Duration		
		1st month	2nd month	3rd month
1	Appearance	White	White	White
2	Hardness (kg/cm^2)	2±0.3	2±0.1	2±0.5
3	The average weight of tablet(mg)	73.8±0.5	73.69±0.4	73.21±0.1
4	Drug content (%)	99.97±0.9%	99.42±0.4%	98.92±0.7%
5	Disintegration Time (min)	25±0.8 secs	21±0.6 secs	22±0.2 secs

Conclusion

The liquisolid compact tablet of Pioglitazone HCl was prepared using a novel carrier Neusilin US 2 and PEG 400 as a solvent with various concentrations. The main goal of the liquisolid compact formulation is to make pioglitazone HCl more soluble. Pure drugs and formulations were studied for solubility. The solubility of the optimized formulation was increased from practically insoluble class to sparingly soluble class. The aqueous solubility of Pioglitazone HCl was increased. The in-vitro dissolution was performed and drug release of F3 was found to be 95.07% after 40 mins. A stability study was performed for 3 months at 40ºC and 75% RH. The drug content was found to be 99.78%, 99.42%, and 98.92% respectively. From the study, we conclude that the solubility of the Pioglitazone HCl was enhanced.

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