

# Novel EDC-Crosslinked Hydroxypropyl banana (*Musa paradisiaca*) starch as a Superdisintegrant for Enhanced Oral Delivery of Pioglitazone Hydrochloride in Orodispersible Tablets

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## ABSTRACT

**Background:** Orally Disintegrating Tablets (ODTs) are gaining attention for improving patient compliance, especially in pediatric, geriatric, and dysphagic populations. **Objective:** This study aimed to develop and evaluate pioglitazone hydrochloride ODTs using EDC-Crosslinked Hydroxypropyl Banana starch (EDC-BS) as a novel, natural superdisintegrant. The objective was to assess the efficiency of EDC-BS in enhancing tablet disintegration and drug release compared to standard formulations containing cross povidone. **Materials and Methods:** EDC-BS was synthesized and characterized to confirm structural modifications and improved physicochemical properties. NMR and HRMS analysis validated effective crosslinking and hydroxyl propylation of banana starch. EDC-BS exhibited superior flowability, compressibility, and swelling capacity compared to native banana starch. Pioglitazone hydrochloride ODT formulations (F1-F10) were evaluated for thickness, hardness, friability, wetting time, disintegration, and *in vitro* drug release. **Results:** Formulations containing EDC-BS (F3 and F4) demonstrated enhanced disintegration efficiency and drug release profiles. Specifically, F3 achieved 96.36% drug release within 10 min and nearly 99.35% within 30 min, comparable to the standard formulation F9 containing crosspovidone. Furthermore, friability and hardness of F3 were within the acceptable range, confirming the mechanical stability of the tablets. **Conclusion:** *In vitro* evaluations highlighted the potential of EDC-BS as a cost-effective and biocompatible superdisintegrant, achieving results comparable to synthetic counterparts while addressing limitations such as cost and environmental concerns. This study establishes EDC-BS as a promising natural alternative for ODT formulations and provides a foundation for further exploration of its applicability in pharmaceutical development.

**Keywords:** Orodispersible tablets, EDC-crosslinked banana starch, Superdisintegrant, Pioglitazone hydrochloride, Drug release, Pharmaceutical formulation.

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**Received:** 18-08-2025;

**Revised:** 03-10-2025;

**Accepted:** 24-12-2025.

## INTRODUCTION

Oral drug delivery is the most widely accepted route of administration due to its convenience, patient compliance, and cost-effectiveness. Among the novel oral drug delivery systems, Orodispersible Tablets (ODTs) have gained prominence due to their ability to disintegrate rapidly in the oral cavity without the need for water. This feature makes ODTs particularly suitable for pediatric, geriatric, and dysphagic populations, who often face challenges with swallowing conventional tablets or capsules.<sup>1</sup>

ODT formulations are particularly beneficial for drugs requiring a rapid onset of action, as their design ensures fast disintegration and dissolution, leading to quicker drug absorption. The effectiveness of ODTs is highly dependent on the inclusion of superdisintegrants, which accelerate the disintegration process. Conventional synthetic super-disintegrants such as cross-povidone, croscarmellose sodium, and sodium starch glycolate are widely used due to their high efficiency. However, these synthetic materials have certain limitations, including high cost, synthetic origins, and, in some cases, potential for adverse effects. These drawbacks have sparked interest in exploring natural polymers as cost-effective, biocompatible, and safer alternatives to synthetic super-disintegrants.<sup>2</sup> Among the natural polymers investigated, starch has gained attention due to its unique physicochemical properties and its ability to be chemically modified to enhance its functionality.<sup>3</sup> Starch



DOI: 10.5530/ijper.20261872

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is a widely available natural polymer known for its excellent swelling and hydration properties, making it a potential candidate for use in pharmaceutical formulations. Banana starch (*Musa paradisiaca*) is particularly notable due to its high amylopectin content, favorable gelatinization behavior, and ease of modification.<sup>3</sup> Starch swelling and gelatinization properties are crucial for their ability to disintegrate in tablets. These properties help starch absorb water quickly and disintegrate, making it effective as a disintegrant in oral tablets. Starches that swell more and gelatinize faster are better at promoting rapid disintegration, which is crucial for improving the dissolution and absorption of drugs, especially poorly soluble ones like pioglitazone. This can lead to better drug release and faster action, making starch an important ingredient in ODT formulations. When starch swells and gelatinizes in a controlled way; it helps release the drug more efficiently. The process also increases the drug's surface area, which speeds up its dissolution and absorption in the body.<sup>4</sup>

Despite these advantages, native starch often lacks the mechanical strength and fast disintegration properties required for use as a superdisintegrant in ODTs. To overcome these limitations, researchers have explored chemical modifications, such as hydroxypropylation and crosslinking, to enhance the functionality of starch. Hydroxypropylation introduces hydroxypropyl groups into the starch structure, increasing its hydrophilicity and swelling capacity. Crosslinking, on the other hand, strengthens the starch granules, improving their resistance to deformation and fragmentation under stress. Crosslinking agents such as 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide (EDC) have been extensively studied for their ability to form stable covalent bonds between polymer chains, further enhancing the mechanical and disintegration properties of starch.<sup>5</sup> However, there is a lack of research on the application of EDC-crosslinked Hydroxypropyl Banana Starch (HPBS) as a superdisintegrant in ODT formulations. Although synthetic superdisintegrants like crosspovidone are highly effective, their high cost and synthetic origins present challenges for widespread use, particularly in resource-limited settings. Furthermore, natural starches, despite their biocompatibility and cost-effectiveness, often require chemical modification to achieve the performance of synthetic superdisintegrants. There is limited research exploring the use of chemically modified banana starch, specifically EDC-crosslinked HPBS, in ODT formulations. This gap in the literature highlights the need to investigate the potential of modified banana starch as an alternative to conventional superdisintegrants.

The development of cost-effective, biocompatible, and efficient natural superdisintegrants is essential for advancing the formulation of ODTs, especially for drugs with poor solubility and bioavailability. Pioglitazone hydrochloride, a widely prescribed antidiabetic drug for managing type 2 diabetes, suffers from poor water solubility, limiting its oral bioavailability.<sup>6</sup> The use of EDC-crosslinked HPBS as a superdisintegrant could

provide a dual benefit by enhancing the rapid disintegration and drug release of pioglitazone ODTs while offering a natural, cost-effective alternative to synthetic superdisintegrants. The hypothesis of this study is that EDC-crosslinked HPBS can function as an efficient superdisintegrant, comparable to or better than synthetic alternatives like crosspovidone, in enhancing the performance of pioglitazone hydrochloride ODTs. The primary objectives of this study are to synthesize and characterize EDC-crosslinked HPBS, formulate pioglitazone hydrochloride ODTs using EDC-crosslinked HPBS as a superdisintegrant, and evaluate and compare the physical properties, disintegration efficiency, and *in vitro* drug release profiles of the formulations with standard formulations containing crosspovidone.

This study focuses on the synthesis, characterization, and application of EDC-crosslinked HPBS as a superdisintegrant in pioglitazone hydrochloride ODTs. The formulations will be assessed for mechanical properties, disintegration time, and drug release performance to determine the feasibility of replacing synthetic superdisintegrants with modified banana starch. While the study is limited to pioglitazone hydrochloride, the findings may have broader implications for the use of EDC-crosslinked HPBS in other Oro dispersible. The paper begins with a comprehensive description of the materials and methods used for the synthesis of EDC-crosslinked HPBS and the formulation of pioglitazone hydrochloride ODTs. This is followed by the characterization of the modified starch and the evaluation of the physical and functional properties of the ODTs. The results are then analyzed and discussed, highlighting the performance of EDC-crosslinked HPBS compared to crosspovidone. The paper concludes with a discussion of the potential applications and limitations of this novel superdisintegrant.

## MATERIALS AND METHODS

### Synthesis of Hydroxypropyl EDC crosslinked BS

#### Preparation of Hydroxypropyl Banana Starch

Banana starch (*Musa paradisiaca* starch) procured from Sri Laxmi Sai Traders, RK Nagar-Malkajgiri, Hyderabad, was Hydroxypropylated using propylene oxide. A 10% (w/v) starch suspension was prepared by dispersing 10 g of starch in 100 mL of distilled water. The pH was adjusted to 11.0 using 1 M sodium hydroxide, and the solution was stirred at 200 rpm. Propylene oxide (10 mL, 15% of starch weight) was added dropwise over 10 min while maintaining pH at 11.0. The reaction was carried out at 40 °C with continuous stirring for 16 hr. Afterward, the mixture was neutralized to pH 7.0 with 1 M hydrochloric acid, centrifuged at 4000 rpm for 10 min, and washed three times with distilled water followed by ethanol. The product was air dried at 40 °C, ground into a fine powder, and stored in an air-tight container for further characterization. The process was performed in triplicate to ensure consistency.<sup>7</sup>

## EDC Crosslinking of Hydroxypropyl Banana Starch

The crosslinking of Hydroxypropyl banana (*Musa paradisiaca*) starch was carried out using 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide (EDC) as the crosslinking agent in the presence of N-Hydroxysuccinimide (NHS) as a coupling enhancer. A 5% (w/v) suspension of hydroxypropylated starch was prepared by dispersing 5 g of starch in 100 mL of distilled water in a glass beaker under constant stirring at 300 rpm. The pH of the suspension was adjusted to 5.5 using 0.1 M hydrochloric acid. EDC (0.2 g, 10% w/w of starch weight) and NHS (0.1 g, 5% w/w of starch weight) were dissolved in 10 mL of distilled water and added dropwise to the starch suspension. The reaction mixture was stirred at room temperature (25 °C) for 6 hr to allow effective crosslinking. The resulting mixture centrifuged at 4000 rpm for 10 min to recover the modified starch, which was subsequently washed three times with distilled water to remove any unreacted reagents. The crosslinked starch was dried in an oven at 40 °C to a constant weight, ground into a fine powder, and stored in a desiccator for further analysis. The process was performed in triplicate to ensure reproducibility. The structural characterization of the modified starch was performed using NMR spectroscopy (<sup>1</sup>H and <sup>13</sup>C) to confirm the presence of hydroxypropylation and crosslinking bonds. Additionally, High-Resolution Mass Spectrometry (HRMS) was utilized to detect molecular weight changes and verify the structural modifications introduced during the hydroxypropylation and EDC crosslinking processes.<sup>8</sup>

## Characterization of EDC-BS

### Morphological Analysis Using SEM

The surface texture and porosity of native starch, Hydroxypropyl starch, and EDC-crosslinked starch were analyzed using Scanning Electron Microscopy (SEM). Dried and finely ground samples (5 mg) were mounted on aluminum stubs with carbon tape and sputter-coated with a 10 nm gold layer at 10 mA for 2 min. Imaging was conducted at 5 kV accelerating voltage and a 10 mm working distance, with magnification of 1000x. The analysis was performed in triplicate to ensure reproducibility.<sup>9</sup>

### Micromeritic Evaluation

The micromeritic properties of the modified starch (EDC-BS) were evaluated to determine flowability and compressibility and was interpreted in reference to Pharmacopoeial standards (Table 1) Bulk density was measured by placing approximately 5 g of dried starch into a 10 mL graduated cylinder and recording the initial volume. Tapped density was obtained by tapping the cylinder 100 times using a USP Type I tapped density tester. Carr's index (%) was calculated using:

$$\text{Carr's Index (\%)} = \left[ \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \right] \times 100$$

The angle of repose ( $\theta$ ) was measured using the fixed funnel method. Approximately 5 g of sample was allowed to flow through a funnel from a height of 2 cm onto a flat surface, forming a conical pile. The Height (h) and Diameter (d) of the pile were measured, and the angle of repose was calculated using:

$$\text{Angle of Repose } (\theta) = \arctan \left( \frac{\text{Height}}{\text{Diameter}/2} \right)$$

All measurements were performed in triplicate at room temperature (25 °C) under standard laboratory conditions to ensure reproducibility. Results were used to evaluate flow and compressibility properties as indicators of the starch's suitability for pharmaceutical applications.<sup>10</sup> Crosspovidone, croscarmellose sodium, and native (unmodified) banana starch were used as reference controls for the study.

## Swelling and Water Absorption Capacity Evaluation

The swelling capacity and water absorption properties of the modified starch (EDC-BS) were evaluated in comparison to native banana starch and native potato starch. Approximately 1 g of each starch sample was accurately weighed and transferred into pre-weighed centrifuge tubes. For swelling-capacity determination, 10 mL distilled water was added to each tube, and the mixtures were allowed to stand at three different temperatures-45°C, 70°C, and 90°C-for 30 min to ensure adequate hydration under varying thermal conditions. The tubes were then centrifuged at 3000 rpm for 10 min. After centrifugation, the supernatant was carefully decanted, and the hydrated starch residue was weighed.

$$\text{Swelling Index (\%)} = \left[ \frac{\text{Weight of swollen Starch} - \text{Initial Dry Weight}}{\text{Initial Dry Weight}} \right] \times 100$$

For water absorption capacity, the starch residues were further dried in an oven at 40 °C to a constant weight and re-weighed.<sup>11</sup> Water absorption capacity was calculated as the percentage increase in weight due to water uptake relative to the initial weight. The experiments were performed in triplicate to ensure reproducibility, and the results were reported as mean  $\pm$  standard deviation.<sup>10</sup>

$$\text{Water Absorption Ratio (\%)} = \left[ \frac{\text{Weight of Hydrated Starch} - \text{Initial Dry Weight}}{\text{Initial Dry Weight}} \right] \times 100$$

Crosspovidone, croscarmellose sodium, and native (unmodified) banana starch were used as reference controls for the study.

## Acute Toxicity Study

Acute toxicity testing of EDC-Crosslinked Banana Starch (EDC-BS) was conducted in Wistar rats following OECD guideline 423. Rats were divided into five groups (A, B, C, D, and E), each comprising four animals (male and female). Group A served as the control group and received normal saline orally. Groups B, C, and D were administered EDC-BS orally at doses

of 500, 1000, and 2000 mg/kg body weight, respectively, after overnight fasting, while Group E received Native Banana Starch (NBS) as the standard at 2000 mg/kg body weight. Food and water were provided ad libitum after administration. Animals were observed continuously for 168 hr for signs of behavioral changes, toxicity, and mortality.<sup>12,13</sup>

### UV Spectroscopic Method of Analysis for Pioglitazone Hydrochloride

The UV spectroscopic analysis was performed to determine its drug content and purity. Standard solutions were prepared at a concentration of 0.5 mg/mL from which working standard solutions were subsequently prepared in the concentration range of 1 to 50 µg/mL using phosphate buffer of pH 6.8 as the solvent. The analysis was conducted using a UV-Visible spectrophotometer (e.g., Shimadzu UV-1800) with data collection and processing managed by the instrument's software. A phosphate buffer of pH 6.8 was used as the solvent to prepare the solutions, ensuring proper solubility of Pioglitazone hydrochloride. The spectrophotometer was calibrated using standard solutions at different concentrations to generate a calibration curve. The absorbance of each solution was measured at 269 nm, the absorption maximum ( $\lambda_{max}$ ) for pioglitazone hydrochloride. The instrument was stabilized by running a blank solution for baseline correction before measurement. Subsequently, the standard solution was analyzed in triplicate to ensure accuracy

and precision. The absorbance values were recorded, and the calibration curve was plotted to confirm linearity. The sample solution, prepared under identical conditions, was analyzed in triplicate. The absorbance values were recorded, and the concentration of pioglitazone hydrochloride in the sample was calculated using the calibration curve. The method ensured reliable quantification of Pioglitazone hydrochloride for further analytical and formulation studies.<sup>14</sup>

### Formulation of Pioglitazone Hydrochloride Tablets

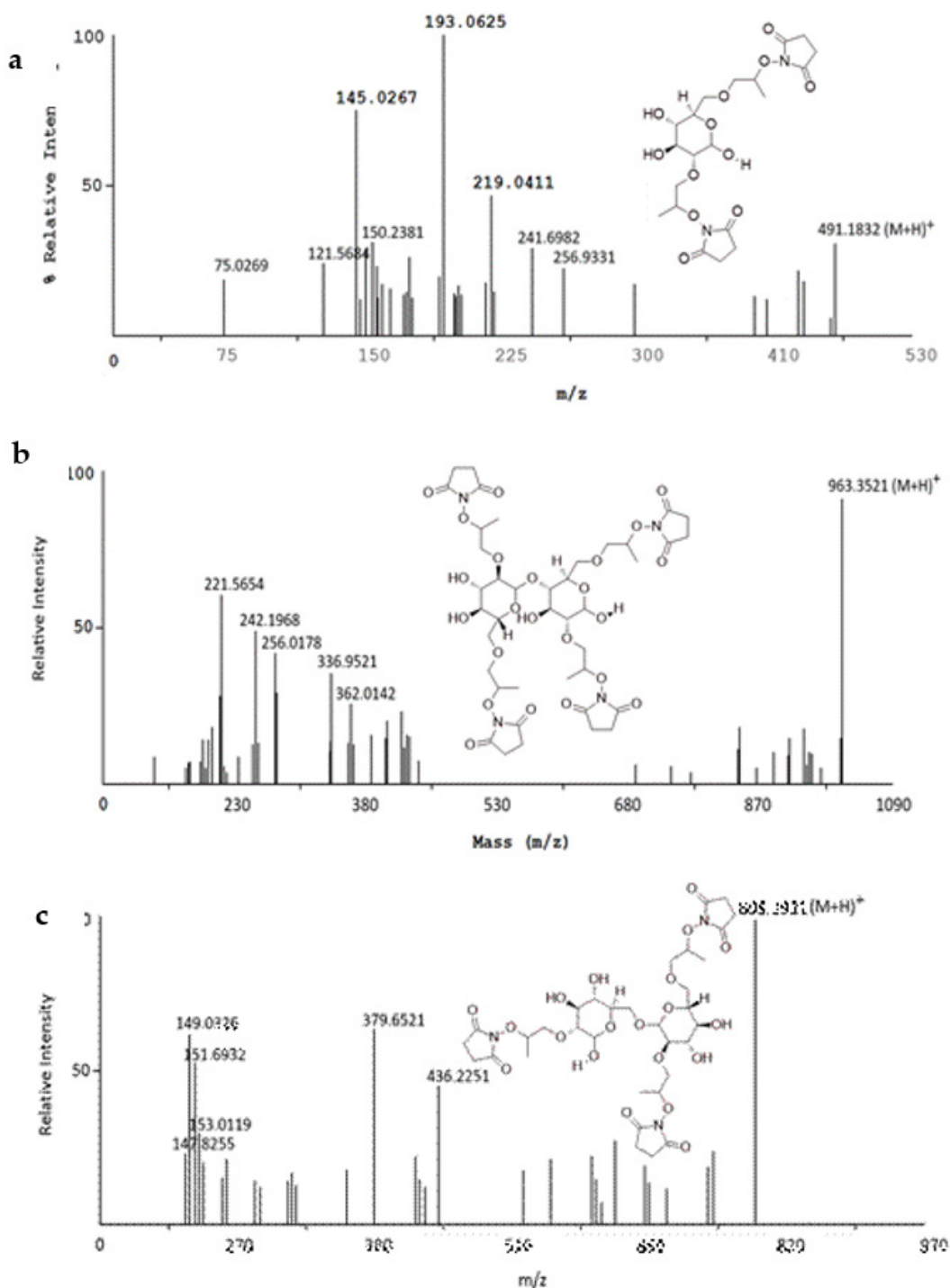
The formulation of pioglitazone hydrochloride tablets was carried out using EDC-crosslinked Banana Starch (BS) as a Disintegrant, Polyvinylpyrrolidone (PVP K30) as a binder, and varying compression forces during tablet compression (Table 2). The concentrations of EDC-crosslinked BS were evaluated at 5% w/w and 15% w/w, while PVP K30 was incorporated at 2% w/w and 5% w/w. A fixed dose of 30 mg of pioglitazone hydrochloride was included per tablet. The tablets were prepared using the wet granulation method. Pioglitazone hydrochloride, EDC-crosslinked banana starch, lactose (used as a diluent), and PVP K30 (binder) were weighed and mixed thoroughly in a mortar and pestle. Distilled water was added dropwise while mixing until a cohesive wet mass was formed. The wet mass was passed through a sieve with 2 mm pore size to obtain granules, which were then dried in a hot air oven at 40 °C for 2 hr. The dried granules were sieved through a 1 mm sieve, and magnesium stearate (0.5% w/w) was added as a lubricant. The granules were compressed into tablets using a rotary tablet press at varying compression forces of 2 kN and 6 kN. The tablets were evaluated for hardness, disintegration time, and dissolution profile to assess the impact of EDC-crosslinked banana starch concentration, binder concentration, and compression force on the quality attributes. All formulations were prepared in triplicate to ensure reproducibility of the results.<sup>15</sup>

**Table 1: Flow Ability Interpretation According to Pharmacopoeial standards.**

Angle of Repose ( $\theta$ )	Flowability
<30°	Excellent flow
30-34°	Good flow
35-40°	Fair flow
>40°	Poor flow

**Table 2: Formulation Details of Pioglitazone Hydrochloride ODTs.**

Formulation	Pioglitazone Hydrochloride (mg)	EDC Cross linked BS (% w/w)	Native BS (% w/w)	Cross Povidone (% w/w)	PVP K30 (% w/w)	Compression Force (kN)
F1	30	5	0	0	2	2
F2	30	5	0	0	5	2
F3	30	15	0	0	2	6
F4	30	15	0	0	5	6
F5	30	0	5	0	2	2
F6	30	0	15	0	5	6
F7	30	0	5	0	2	2
F8	30	0	15	0	5	6
F9	30	0	0	15	2	2
F10	30	0	0	15	5	6



**Figure 1:** HRMS spectra of EDC-crosslinked glucose monosaccharide units from BS (a), EDC-crosslinked glucose disaccharide units with 1,4- $\alpha$  glycosidic bonds from BS (b), and EDC-crosslinked glucose disaccharide units with 1,6- $\alpha$  glycosidic bonds from BS (c), representative of their (M+H)<sup>+</sup> ions.

## Characterization of Pioglitazone Hydrochloride ODTs

### Hardness Testing

Hardness testing was conducted on 10 tablets from each batch, including all ODTs of pioglitazone hydrochloride containing tablets (10 formulations) as outlined in the table. Tablets were selected free of visible defects and stored under controlled

conditions. Using a calibrated tablet hardness tester, force was gradually applied to each tablet until it broke, and the breaking force was recorded in kg/cm<sup>2</sup>. This process was repeated for all 10 tablets per batch. The average hardness and standard deviation were calculated for each batch and compared to the acceptable ODT range (2-8 kp). Special focus was given to the performance of EDC crosslinked BS formulations relative to other formulations.

### Thickness, Diameter, and Wetting Time Measurement

The thickness and diameter of the formulated tablets (F1 to F10) were measured using a digital Vernier caliper to ensure uniformity among all formulations. Ten tablets from each formulation batch were randomly selected, and their individual thickness and diameter were recorded. The measurements were carried out under standard laboratory conditions, ensuring the absence of external pressure during the readings to prevent deformation. The wetting time for the orodispersible tablets was determined using a method designed to simulate *in vivo* conditions. A Petri dish with a diameter of 10 cm was filled with 10 mL of distilled water containing a small quantity of eosin dye to enhance visibility. Each tablet was carefully placed on the surface of the dyed water, and the time taken for the water to completely penetrate and get wet the tablet was recorded using a stopwatch. The test was performed at room temperature ( $25\pm 2^\circ\text{C}$ ) and was conducted in triplicate for each formulation to ensure reproducibility and reliability of the results. Wetting time is a critical parameter for orodispersible tablets as it reflects their ability to rapidly disintegrate upon contact with moisture.

### Friability Testing

Friability testing was conducted on 20 tablets from each batch of including all ODTs of pioglitazone hydrochloride containing tablets (10 formulations) as specified in the table. Tablets were gently cleaned to remove dust or loose particles and weighed to determine the initial weight ( $W_{\text{initial}}$ ). The tablets were then placed in a friability tester drum and subjected to 100 rotations at 25 rpm over 4 min. After testing, broken fragments and dust were sieved out using a 60-mesh sieve, and the tablets were reweighed to determine the final weight ( $W_{\text{final}}$ ). The friability percentage was calculated using the formula:

$$\text{Friability (\%)} = \frac{(W_{\text{initial}} - W_{\text{final}})}{W_{\text{initial}}} \times 100$$

The initial and final weights, as well as the friability percentage for each batch, were documented. The acceptable limit for friability was typically less than 1%, and any tablets with friability greater than 1% indicated poor durability, necessitating formulation adjustments. By performing these tests, the mechanical strength and durability of the ODTs were confirmed, ensuring they could withstand packaging and transportation stresses while disintegrating quickly when administered.

### Determination of Disintegration time

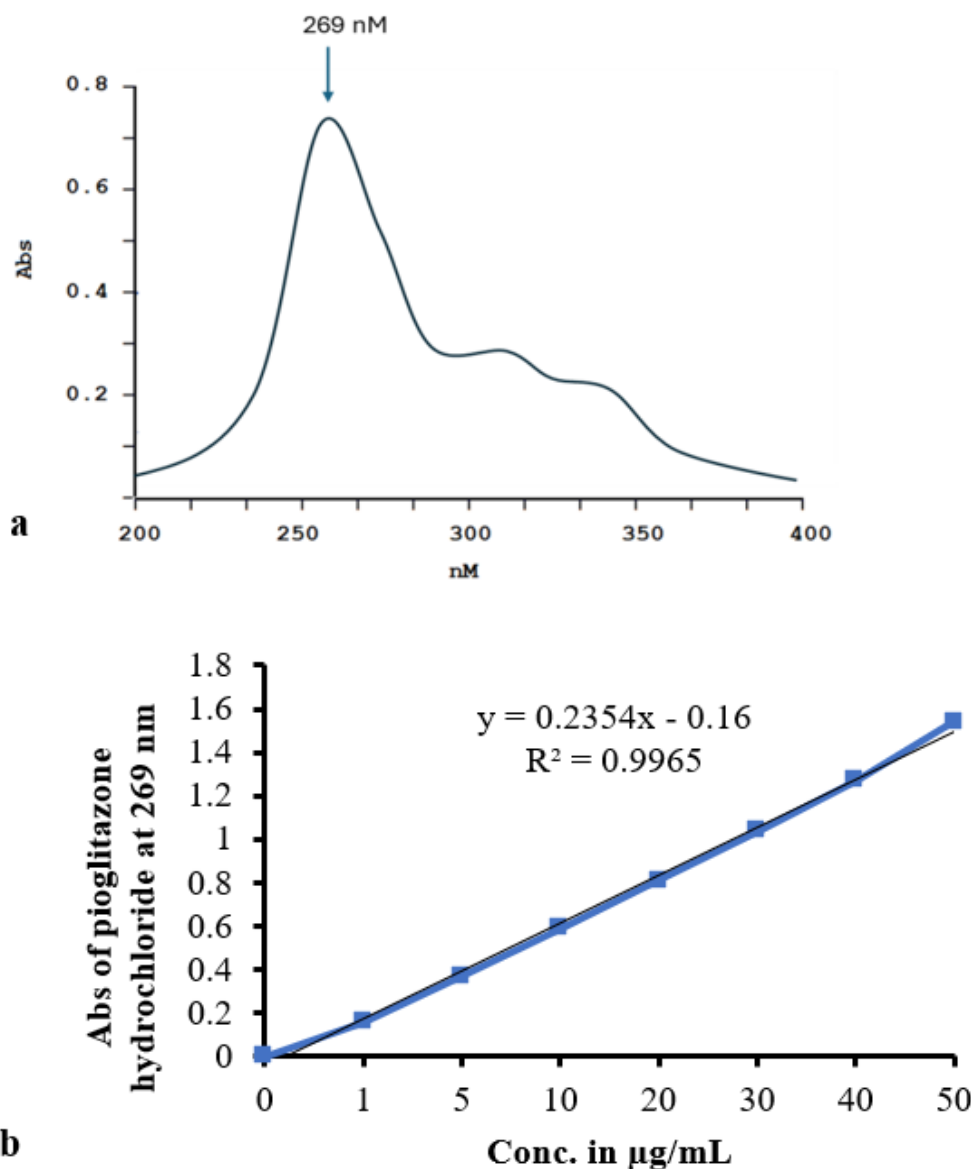
The disintegration time of pioglitazone hydrochloride ODTs was evaluated for formulations F1 to F10. The test was performed using a USP-compliant disintegration apparatus with a 1000 mL beaker filled with distilled water maintained at  $37\pm 2^\circ\text{C}$ , as per USP <701> specifications. Six tablets from each formulation were placed individually into the tubes of the basket-rack assembly, which was then immersed in the medium. The apparatus was operated at a frequency of 29-32 cycles per minute to simulate physiological conditions. Disintegration was considered complete when no residue of the tablet remained on the screen of the basket. The time required for each of the six tablets to completely disintegrate was measured using a stopwatch, and the mean disintegration time for each formulation was calculated. Table A control formulation containing potato starch as the superdisintegrant was tested under the same conditions. The results were compared with those of the EDC-crosslinked banana starch formulations to assess disintegration enhancement.

### In vitro Drug Release Profile

*In vitro* drug release studies were conducted for formulations F3, F4, F9, and F10 containing modified banana starch, as well as a control formulation containing potato starch, to evaluate the release profile of pioglitazone hydrochloride. The study aimed to compare the drug release behavior of the modified banana starch formulations with the conventional potato starch formulation. Dissolution testing was performed using a USP Type II (paddle) dissolution apparatus (e.g., Electrolab TDT-08L). The dissolution medium comprised 900 mL of phosphate buffer (pH 6.8) maintained at  $37\pm 0.5^\circ\text{C}$  to simulate physiological conditions. The paddle speed was set to 50 rpm to ensure a consistent environment. Six tablets from each formulation were placed individually in the dissolution vessels containing the preheated medium. At predetermined intervals (5, 10, 15, 20, 30, 45, and 60 min), 5 mL samples were withdrawn using a syringe fitted with a filter to remove undissolved particles. An equal volume of fresh medium maintained at the same temperature was immediately added to maintain a constant volume. The withdrawn samples were analyzed for pioglitazone hydrochloride content using a UV-visible spectrophotometer (e.g., Shimadzu UV-1800) at 269 nm, the absorption maximum for pioglitazone hydrochloride. Calibration curves prepared with standard solutions ensured accurate quantification. The percentage of drug released at

**Table 3: Micromeritic evaluation of various starch forms.**

Starch Variant	Angle of Repose (degrees)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)
EDC-BS	27.35 $\pm$ 1.24	0.41 $\pm$ 0.02	0.47 $\pm$ 0.03	13.52 $\pm$ 0.51
Native BS	33.12 $\pm$ 1.58	0.63 $\pm$ 0.01	0.78 $\pm$ 0.01	22.81 $\pm$ 0.74
Native Potato starch	29.49 $\pm$ 1.92	0.47 $\pm$ 0.03	0.55 $\pm$ 0.04	18.27 $\pm$ 0.58
Crosspovidone	28.53 $\pm$ 1.89	0.49 $\pm$ 0.01	0.52 $\pm$ 0.02	20.14 $\pm$ 0.85



**Figure 2:** (a) UV spectrum of pioglitazone hydrochloride showing a maximum absorption peak at 269 nm, confirming its characteristic wavelength; (b) Calibration curve of pioglitazone hydrochloride at 269 nm, demonstrating linearity ( $R^2=0.9965$ ) over the concentration range of 1-50  $\mu\text{g/mL}$ .

each time point was calculated using the absorbance values and plotted against time to generate the release profile for each formulation. Comparison of the release profiles demonstrated the effectiveness of modified banana starch in enhancing drug release, providing valuable insights into its potential advantages as a superdisintegrant in pioglitazone hydrochloride ODTs.

### Statistical Analysis

All experimental data were analyzed using statistical methods to determine the significance of variations between formulations. Results were expressed as mean values, and standard deviations were calculated. Comparative analyses were performed using one-way ANOVA followed by *post hoc* tests where applicable,

with a significance level set at  $p < 0.05$ . Statistical analysis was conducted using GraphPad Prism.

## RESULTS AND DISCUSSION

### Preparation and Structural Characterization of EDC-Crosslinked Banana Starch

The composition and structural characteristics of banana starch were analyzed, highlighting its primary components, amylose and amylopectin. Amylose consists of linear chains of glucose linked by 1,4- $\alpha$ -glycosidic bonds, while amylopectin is a branched polysaccharide with both 1,4- $\alpha$  and 1,6- $\alpha$ -glycosidic bonds.<sup>16,17</sup> Compared to potato starch, banana starch has lower amylose content and a more compact granule structure, influencing its

enzymatic digestion and chemical reactivity.<sup>3</sup> During digestion, amylose and amylopectin produce glucose disaccharides with 1,4- $\alpha$ -glycosidic linkages, while the branching points in amylopectin yield glucose disaccharides with 1,6- $\alpha$ -glycosidic linkages. These glucose units played a critical role in forming the EDC-crosslinked derivatives, where the hydroxyl groups participated in crosslinking reactions to produce modified starch structures.<sup>18,19</sup> The banana starch was hydroxypropylated to enhance hydrophilicity and subsequently crosslinked using EDC (1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide) and NHS (N-Hydroxysuccinimide) under optimized conditions. Approximately 67% of the starch underwent crosslinking, as evidenced by a reduction in unreacted hydroxyl groups compared to the initial starch. This crosslinking resulted in covalent bonds between glucose units of amylose and amylopectin, enhancing the structural stability of the starch network of amylopectin.<sup>19,20</sup> Structural validation was performed using proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) NMR spectroscopy and the structural characterization was shown in Figure 1. For monosaccharide units, <sup>1</sup>H NMR signals between  $\delta$  1.24-6.12 ppm confirmed the presence of glucose structures, while <sup>13</sup>C NMR peaks at  $\delta$  95.72 and  $\delta$  80.44 ppm indicated the anomeric carbons involved in glycosidic linkages.<sup>20</sup> Disaccharide units with 1,4- $\alpha$  glycosidic bonds showed <sup>1</sup>H NMR peaks at  $\delta$  3.8-4.1 ppm for glycosidic linkages and distinct signals at  $\delta$  4.78-5.01 ppm for EDC-mediated crosslinking, with <sup>13</sup>C NMR signals at  $\delta$  95.75 and  $\delta$  80.88 ppm confirming the anomeric carbons.<sup>17,18</sup> Similarly, for disaccharide units with 1,6- $\alpha$  glycosidic bonds, <sup>1</sup>H NMR peaks at  $\delta$  3.47-4.98 ppm and <sup>13</sup>C NMR peaks at  $\delta$  101.88 and  $\delta$  80.45 ppm confirmed the glycosidic linkages and branching points of amylopectin.<sup>16,20</sup> High-Resolution Mass Spectrometry (HRMS) further validated the molecular weights of EDC-crosslinked derivatives. Monosaccharide units showed a molecular ion at  $m/z$  491.1832, consistent with theoretical mass calculations (Figure 1a). Disaccharide units with 1,4- $\alpha$  glycosidic bonds exhibited a molecular ion at  $m/z$  963.3521 (Figure 1b), while those with 1,6- $\alpha$  glycosidic bonds showed a molecular ion at  $m/z$  808.2931 (Figure 1c), confirming successful crosslinking.<sup>21</sup> Collectively, these results demonstrate the successful modification of banana starch through EDC/NHS crosslinking, as validated by detailed spectroscopic and mass spectrometric analyses. The structural modifications enhance the functional properties of banana starch, establishing its potential as an advanced biomaterial for pharmaceutical and industrial applications.

EDC-glucose (Monosaccharide): <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.244 (dd,  $J=4.557$ , 6.846 Hz, 6H), 2.683-2.810 (m, 8H), 3.470 (dq,  $J=6.570$ , 6.570, 6.779, 10.565 Hz, 3H), 3.591 (tt,  $J=5.537$ , 5.537, 11.836, 11.836 Hz, 4H), 3.663 (pent,  $J=5.860$ , 5.860, 5.903, 5.903 Hz, 1H), 3.737 (dd,  $J=7.097$ , 12.362 Hz, 1H), 3.846 (dd,  $J=7.093$ , 12.358 Hz, 1H), 3.945 (hept,  $J=6.868$ , 6.868, 6.868, 6.868, 6.968, 6.968 Hz, 2H), 4.170 (d,  $J=3.927$  Hz, 1H), 4.310 (d,  $J=3.629$  Hz, 1H), 4.960-5.019 (m, 1H), 6.124 (d,  $J=5.037$  Hz, 1H); <sup>13</sup>C NMR (125 MHz, DMSO- $d_6$ )  $\delta$  171.96, 171.94, 171.92,

95.72, 80.44, 74.46, 74.25, 73.48, 73.23, 72.44, 71.71, 71.56, 69.76, 39.53, 25.34, 16.77, 16.69; HRMS: (M+H)<sup>+</sup>for C<sub>10</sub>H<sub>30</sub>N<sub>2</sub>O<sub>12</sub> Cal. 491.1871, found 491.1832.

EDC-disaccharide glucose (1,4- $\alpha$  glycosidic): <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.245 (dd,  $J=4.958$ , 6.884 Hz, 12H), 2.684-2.810 (m, 16H), 3.435-3.791 (m, 19H), 3.846 (dd,  $J=6.973$ , 12.359 Hz, 2H), 3.945 (hept,  $J=6.916$ , 6.916, 6.961, 6.961, 6.961, 6.961 Hz, 4H), 4.130 (dd,  $J=4.794$ , 30.399 Hz, 2H), 4.788 (d,  $J=6.723$  Hz, 1H), 5.012 (dd,  $J=4.914$ , 6.966 Hz, 1H), 6.120 (s, 1H); <sup>13</sup>C NMR (125 MHz, DMSO- $d_6$ )  $\delta$  172.19, 172.14, 172.10, 172.08, 172.05, 172.03, 171.99, 171.94, 101.08, 95.75, 80.88, 80.85, 79.15, 74.76, 74.55, 74.50, 74.46, 74.25, 73.80, 73.66, 72.72, 72.46, 72.44, 71.65, 71.56, 71.38, 70.86, 69.71, 39.57, 25.35, 25.34, 16.80, 16.78, 16.69; HRMS: (M+H)<sup>+</sup>for C<sub>40</sub>H<sub>58</sub>N<sub>4</sub>O<sub>23</sub> Cal. 963.3564, found 963.3521.

EDC-disaccharide glucose (1,6- $\alpha$  glycosidic): <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ )  $\delta$  1.244 (dd,  $J=4.752$ , 6.912 Hz, 9H), 2.747 (h,  $J=5.594$ , 5.594, 5.723, 5.723 Hz, 12H), 3.475 (q,  $J=7.195$ , 7.207, 7.207 Hz, 4H), 3.610 (dtd,  $J=6.162$ , 12.068, 12.171, 23.037 Hz, 9H), 3.748 (ddt,  $J=5.951$ , 5.951, 9.396, 12.393 Hz, 2H), 3.846 (dd,  $J=6.912$ , 12.319 Hz, 2H), 3.899-4.004 (m, 4H), 4.103 (d,  $J=5.037$  Hz, 1H), 4.166 (t,  $J=4.686$ , 4.686 Hz, 2H), 4.310 (d,  $J=4.141$  Hz, 1H), 4.594 (d,  $J=7.111$  Hz, 1H), 4.982 (dd,  $J=4.972$ , 6.473 Hz, 1H), 6.124 (d,  $J=5.010$  Hz, 1H); <sup>13</sup>C NMR (125 MHz, DMSO- $d_6$ )  $\delta$  172.05, 172.01, 171.99, 171.96, 171.94, 171.87, 101.88, 95.72, 80.45, 80.23, 74.52, 74.51, 74.46, 74.30, 74.06, 73.52, 73.23, 72.44, 71.65, 71.60, 71.50, 71.35, 69.71, 67.94, 39.57, 25.35, 16.78, 16.77, 16.69; HRMS: (M+H)<sup>+</sup>for C<sub>33</sub>H<sub>49</sub>N<sub>3</sub>O<sub>20</sub> Cal. 808.2982 found 808.2931.

## Characterization of EDC-BS

### SEM analysis

The SEM analysis of native Banana Starch (BS) and EDC-Crosslinked Banana Starch (EDC-BS) revealed distinct

**Table 4: Degree of swelling.**

Crosslinking Degree	Temperature	Degree of Swelling (%)
EDC-BS Starch	45°C	114%
EDC-BS MP Starch	70°C	139%
EDC-BS MP Starch	90°C	159%
Native BS Starch	45°C	107%
Native BS Starch	70°C	127%
Native BS Starch	90°C	131%
Native Potato Starch	45°C	109%
Native Potato Starch	70°C	129%
Native Potato Starch	90°C	135%
Crosspovidone	45°C	111%
Crosspovidone	70°C	132%
Crosspovidone	90°C	141%

differences in surface morphology and porosity. Native BS exhibited smooth, compact granules with minimal porosity, characteristic of unmodified starch. In contrast, EDC-BS showed rough, irregular surfaces and increased porosity, indicative of structural disruptions caused by hydroxypropylation and subsequent EDC/NHS crosslinking. The observed porosity enhancement suggests improved hydrophilicity and water absorption, which are critical for applications such as pharmaceutical formulations. The rough surface morphology of EDC-BS reflects the formation of covalent bonds between hydroxyl groups in glucose units of amylose and amylopectin during the crosslinking process. These structural changes are consistent with previous findings on chemically modified starches.<sup>8</sup> The reproducibility of the SEM analysis, performed in triplicate, validate the reliability of these observations. The enhanced porosity and surface area of EDC-BS demonstrate its improved functional properties, supporting its application as an advanced biomaterial.

### Micromeritic Evaluation of EDC-BS

The micromeritic properties of EDC-BS, native Banana Starch (native BS), native potato starch, and crosspovidone were evaluated (Table 3). EDC-BS showed an angle of repose of  $27.35 \pm 1.24^\circ$ , classifying it under “excellent flow” as per pharmacopoeial limits. This was comparable to crosspovidone ( $28.53 \pm 1.89^\circ$ ) and native potato starch ( $29.49 \pm 1.92^\circ$ ), both also falling within the excellent flow category. In contrast, native BS exhibited a higher angle ( $33.12 \pm 1.58^\circ$ ), corresponding to “good flow”. The improved flow behavior of EDC-BS can be attributed to crosslinking, which disrupts the granular structure of native starch and introduces modifications that reduce interparticle friction and cohesion.<sup>19</sup> The bulk density of EDC-BS was  $0.41 \pm 0.02$  g/mL, lower than that of native BS ( $0.63 \pm 0.01$  g/mL) and native potato starch ( $0.47 \pm 0.03$  g/mL). Its tapped density, recorded at  $0.47 \pm 0.03$  g/mL, displayed a closer correlation with its bulk density compared to native BS, which had significantly higher tapped density values ( $0.78 \pm 0.01$  g/mL). The lower bulk and tapped densities observed in EDC-BS reflect its porous structure, which likely results from crosslinking and leads to improved compressibility.<sup>18</sup>

Carr’s index further confirmed the enhanced compressibility of EDC-BS ( $13.52 \pm 0.51\%$ ), classifying it as “good to excellent” (Pharmacopoeial threshold:  $<15\%$ =good flow), compared to native BS ( $22.81 \pm 0.74\%$ ) and native potato starch ( $18.27 \pm 0.58\%$ ). Crosspovidone had a Carr’s index of  $20.14 \pm 0.85\%$ , reinforcing EDC-BS’s superior micromeritic profile. The lower Carr’s index for EDC-BS highlights the enhanced particle morphology and decreased interparticle friction achieved through crosslinking. These improvements align with previous findings on chemically modified starches, where crosslinking enhances the functional properties of starch.<sup>3</sup> The superior micromeritic properties of EDC-BS compared to native BS suggest its potential as an advanced excipient for pharmaceutical applications. Its

comparable performance to crosspovidone further demonstrates its viability as a biodegradable and cost-effective alternative for tablet formulations.<sup>16,19</sup> These values suggest that EDC-BS exhibits pharmaceutical-grade flow and compressibility properties, making it a promising biodegradable excipient.

### Degree of swelling

The Degree of Swelling (DS) of EDC-Crosslinked Banana Starch (EDC-BS) was significantly higher than that of Native banana starch (native BS), native potato starch, and comparable to crosspovidone at all tested temperatures ( $45^\circ\text{C}$ ,  $70^\circ\text{C}$ , and  $90^\circ\text{C}$ ) and the results were shown in Table 4. At  $90^\circ\text{C}$ , EDC-BS exhibited the highest DS of 159%, outperforming native BS (131%) and native potato starch (135%), and closely approaching crosspovidone (141%). At  $70^\circ\text{C}$ , EDC-BS showed a DS of 139%, native BS, and native potato starch (129%). Even at  $45^\circ\text{C}$ , EDC-BS (114%) demonstrated better swelling than native BS (107%) and native potato starch (109%). The enhanced swelling of EDC-BS can be attributed to the crosslinking process, which introduces hydrophilic groups while maintaining structural integrity, facilitating water absorption and retention. This is consistent with earlier findings that crosslinking improves the hydrophilicity of starches.<sup>19</sup> Compared to native starches, the structural stabilization achieved through EDC/NHS crosslinking likely enhanced the accessibility of amylose and amylopectin chains to water, resulting in greater swelling capacity.<sup>18</sup> Although crosspovidone exhibited the highest DS, the performance of EDC-BS at higher temperatures highlights its potential as a competitive and biodegradable alternative for applications requiring efficient water absorption, such as in pharmaceutical formulations for orodispersible tablets.<sup>16</sup>

### Water Absorption Capacity

The Water Absorption Capacity (WAC) of EDC-Crosslinked Banana Starch (EDC-BS) was the highest among all samples, reaching 261.3%, surpassing native potato starch (236.5%), crosspovidone (248.9%), and native banana starch (186.7%) as shown in Table 5. The enhanced WAC of EDC-BS is attributed to the introduction of hydrophilic groups and increased porosity due to EDC/NHS crosslinking. Native banana starch displayed the lowest WAC, reflecting its compact granular structure, while native potato starch exhibited higher WAC due to its naturally porous structure and higher amylopectin content.<sup>16</sup> The superior performance of EDC-BS compared to crosspovidone underscores

**Table 5: Water absorption capacity (%) of various starch forms.**

Sample	Water Absorption Capacity (WAC) in %
EDC-BS Starch	261.3
Native BS Starch	186.7
Native Potato Starch	236.5
Crosspovidone	248.9

its potential as an effective and biodegradable excipient for pharmaceutical formulations, especially in orodispersible tablets requiring rapid hydration. These findings align with previous studies reporting improved hydrophilicity and functionality in chemically modified starches.<sup>18,19</sup>

### Acute toxicity studies

Acute toxicity studies in Wistar rats demonstrated the safety of EDC-BS and Native Banana Starch (NBS) at doses of 500, 1000, and 2000 mg/kg body weight over 24, 48, 72, and 168 hr. All the results were shown in Tables 6 and 7. No significant weight loss or adverse effects were observed in any group, confirming the non-toxic nature of both starch derivatives at the tested doses. At 500 mg/kg (Group B), EDC-BS resulted in body weights comparable to the control group (Group A) throughout the study, reaching 25.13±1.2 g at 168 hr. At 1000 mg/kg (Group C), body weights increased further, reaching 27.47±2.6 g. The highest dose of 2000 mg/kg (Group D) also showed no toxicity, with body weight rising to 28.96±1.9 g (Table 6). Similarly, the NBS-treated group (Group E) showed no adverse effects, with body weight reaching 27.84±1.9 g at 168 hr. The absence of adverse effects or significant weight changes across all groups, even at the highest dose, demonstrating excellent biocompatibility and safety of EDC-BS. These findings align with previous studies reporting minimal toxicity and high biocompatibility for chemically modified starches.<sup>18,19</sup> The structural stability provided by EDC crosslinking, combined with the natural biodegradability of starch, makes EDC-BS a promising candidate for pharmaceutical applications. This study highlights EDC-BS as a safe and effective alternative to conventional excipients, with potential for further exploration in drug delivery systems. Long-term toxicity and pharmacokinetic studies are recommended to fully validate its suitability for pharmaceutical applications. The evaluation of EDC-BS and NBS at doses of 500, 1000, and 2000 mg/kg body weight over 24, 48, 72, and 168 hr revealed no significant behavioral changes, toxic effects, or mortality. Behavioral parameters, including gross activity, salivation, and sense of touch and sound, remained normal across all groups, with no observed convulsions, abnormal urination, diarrhea, or mortality. The consistent absence of adverse effects across all treatment groups indicates the safety and biocompatibility of EDC-BS and

NBS, even at the highest dose of 2000 mg/kg. These findings align with previous studies highlighting the non-toxic nature of chemically modified starches due to their biodegradability.<sup>18,19</sup> EDC crosslinking did not compromise the safety profile of banana starch, supporting its potential use in pharmaceutical applications such as orodispersible tablets.

### UV Spectrometric Analysis of Pioglitazone Hydrochloride

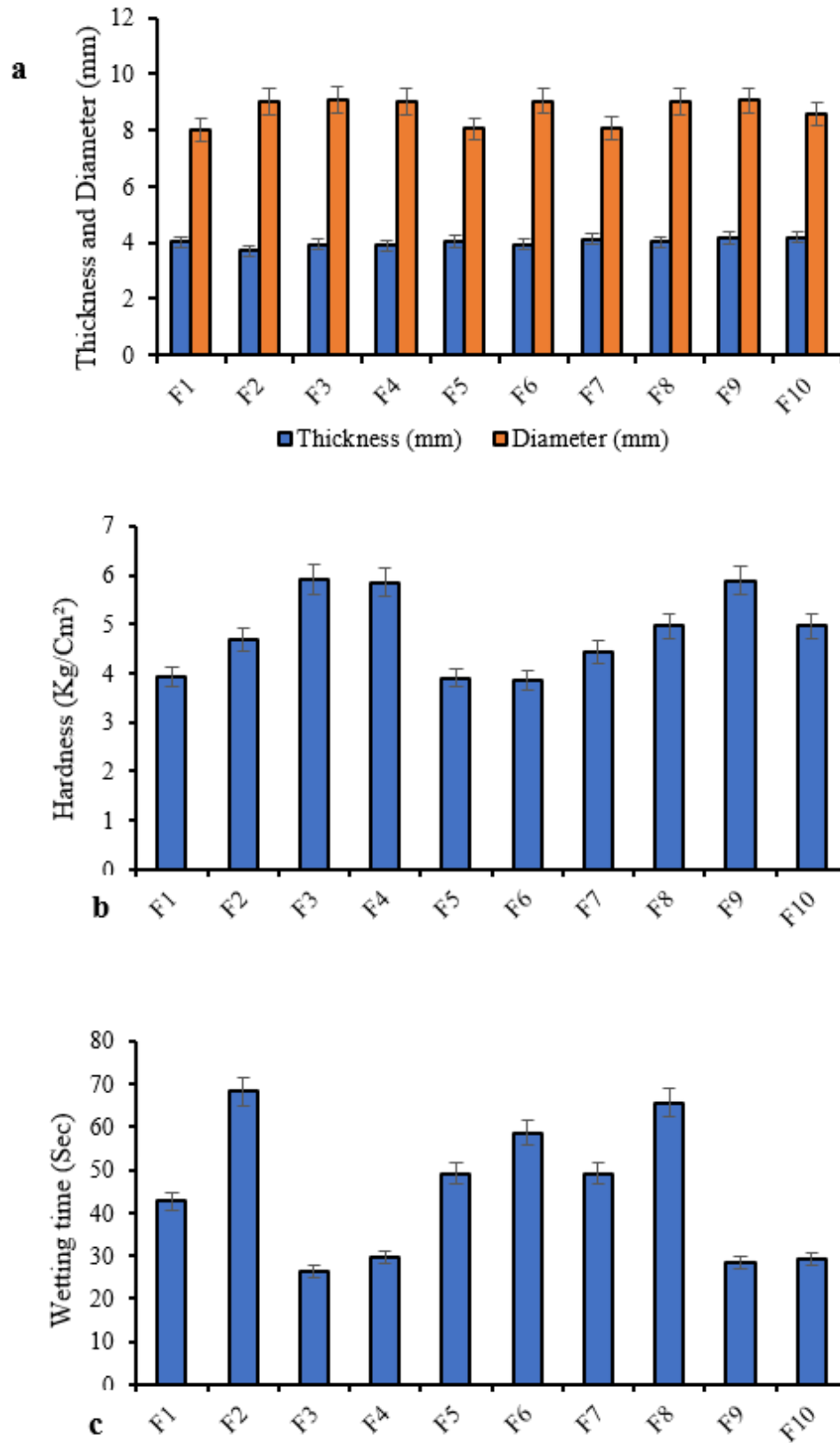
The UV spectroscopic analysis of pioglitazone hydrochloride was performed to determine its  $\lambda_{\max}$  content, and purity. The absorption spectrum revealed a maximum absorbance ( $\lambda_{\max}$ ) at 269 nm (Figure 2a), confirming the characteristic absorption of pioglitazone hydrochloride in the phosphate buffer (pH 6.8). This finding aligns with previously reported values for the compound.<sup>14</sup> A calibration curve was constructed using standard solutions prepared at concentrations ranging from 1 to 50 µg/mL, with absorbance measured at 269 nm (Figure 2b). The calibration plot demonstrated excellent linearity with a regression coefficient ( $R^2$ ) of 0.9965, indicating a strong correlation between concentration and absorbance. The regression equation was calculated as  $y=0.2354x-0.16$ , providing a reliable basis for quantifying pioglitazone hydrochloride in subsequent analyses. Triplicate analysis of both standard and sample solutions ensured precision and reproducibility, with minimal variation in absorbance values. The high degree of linearity and reproducibility highlights the accuracy of the method, making it suitable for analytical and formulation studies. This approach enables reliable quantification of pioglitazone hydrochloride for its incorporation in pharmaceutical formulations.

### Formulation of Pioglitazone Hydrochloride Orodispersible Tablets

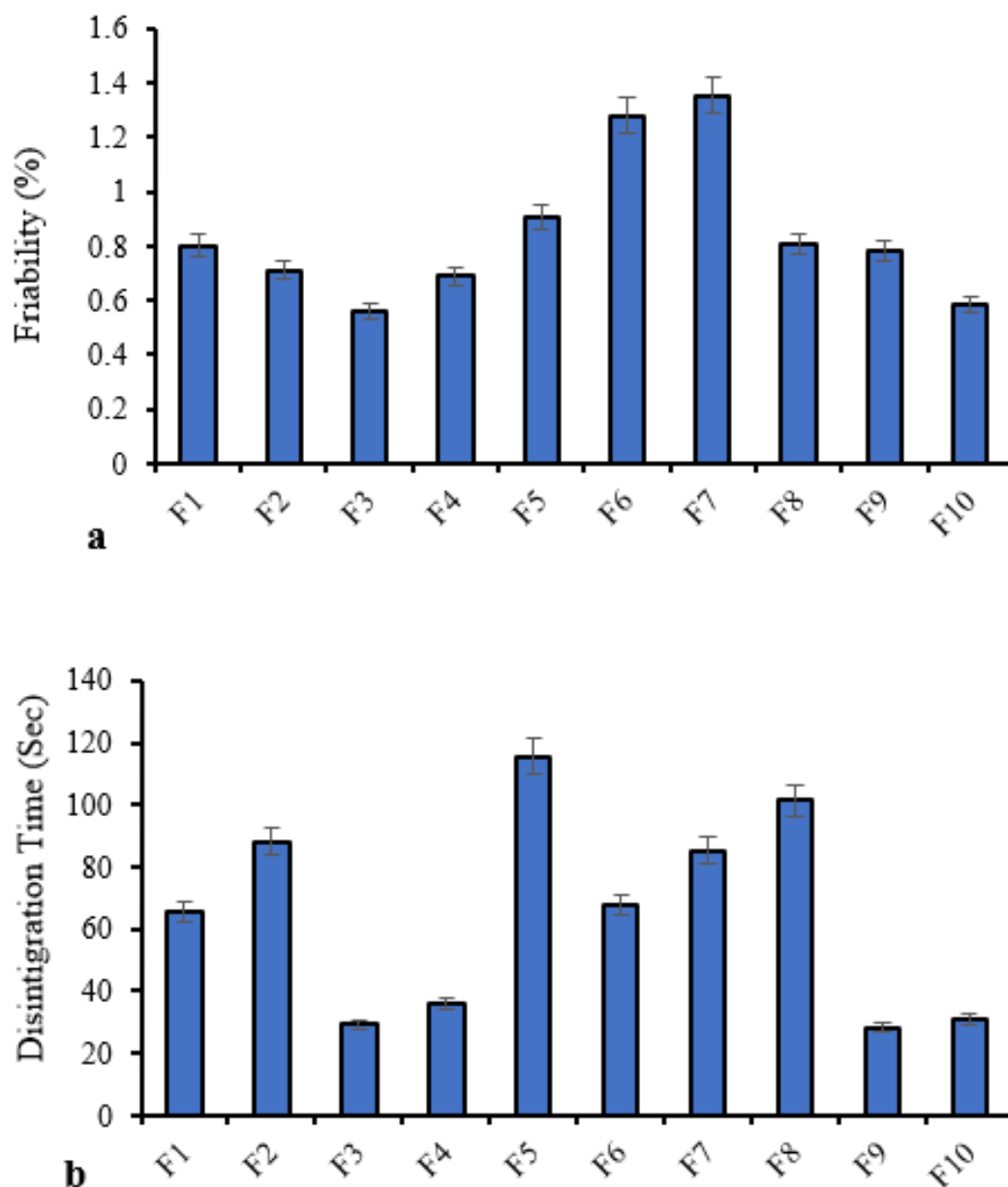
Pioglitazone hydrochloride Orodispersible Tablets (ODTs) were formulated using EDC-Crosslinked Banana Starch (EDC-BS) as a superdisintegrant. Variations in EDC-BS concentration (5% and 15% w/w), binder (PVP K30 at 2% and 5% w/w), and compression force (2 kN and 6 kN) were evaluated. Tablets with 15% w/w EDC-BS (F3, F4) demonstrated superior disintegration and dissolution profiles compared to those with Native Banana Starch (NBS) or cross-povidone. EDC-BS tablets

**Table 6: Effect EDC-BS on bodyweight changes during acute toxicity studies.**

Treatment duration (hrs)	Body weight (g)				
	Group A (Control)	Group B (EDC-BS @ 500 mg/kg bw)	Group C (EDC-BS @ 1000 mg/kg bw)	Group D (EDC-BS @ 2000 mg/kg bw)	Group E (NBS @ 2000 mg/kg bw)
24 hr	24.18±1.6	24.23±1.1	24.29±1.8	24.22±1.2	24.17±1.2
48 hr	24.22±1.2	24.34±1.5	25.71±2.2	24.89±2.1	24.55±2.1
72 hr	24.35±1.9	24.39±1.4	25.96±1.4	25.71±1.5	25.98±1.5
168 hr	24.79±1.1	25.13±1.2	27.47±2.6	28.96±1.9	27.84±1.9



**Figure 3:** (a) Comparative evaluation of thickness (mm) and diameter (mm) for formulations F1-F10, showing consistent dimensional properties across all formulations; (b) Hardness (Kg/cm<sup>2</sup>) of formulations F1-F10, indicating mechanical strength suitable for orodispersible tablets; (c) Wetting time (seconds) of formulations F1-F10, demonstrating variations in disintegration efficiency among formulations. Error bars represent standard deviations.



**Figure 4:** (a) Friability (%) of formulations F1-F10, indicating the mechanical stability of the orodispersible tablets, with formulations F6 and F7 exceeding the pharmacopoeial limit of 1%; (b) Disintegration time (seconds) of formulations F1-F10, highlighting variations in rapid disintegration efficiency, with F3, F4, F9, and F10 meeting the ideal time for orodispersible tablets. Error bars represent standard deviations.

achieved over 90% drug release within 15 min, highlighting their rapid disintegration and dissolution efficiency. Binder concentration and compression force significantly influenced tablet properties. Tablets containing 5% w/w PVP K30 exhibited higher hardness but slightly slower disintegration, while lower binder concentration (2% w/w) resulted in faster disintegration but reduced mechanical strength. Higher compression force (6 kN) enhanced hardness but slightly delayed disintegration due to reduced porosity. Formulations F3 and F4, containing 15% w/w EDC-BS and 5% w/w PVP K30, provided an optimal balance of rapid disintegration and mechanical strength, making EDC-BS

a promising biodegradable alternative to conventional synthetic superdisintegrants.

### Characterization of Pioglitazone Hydrochloride ODTs Thickness, diameter, hardness, wetting time measurements

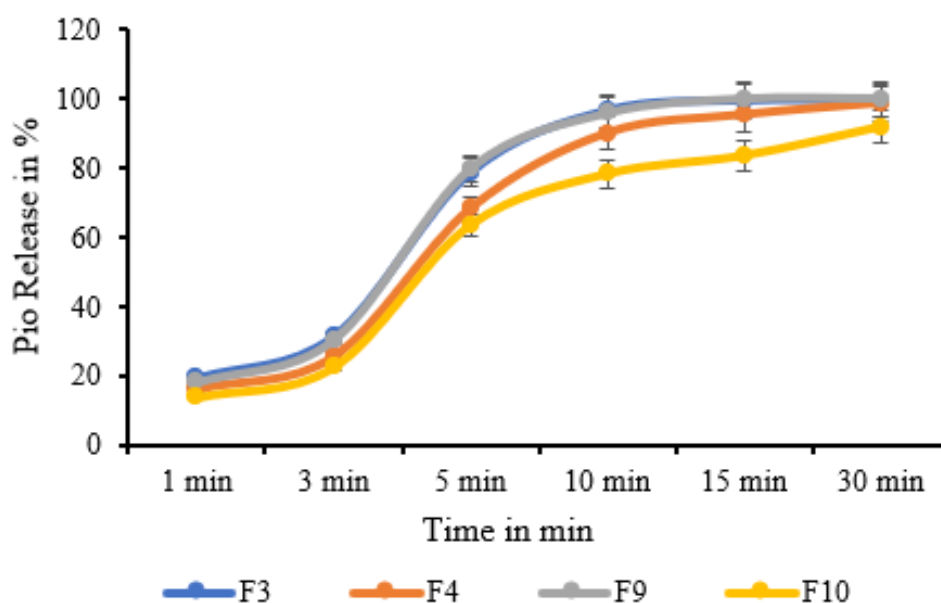
The evaluation of pioglitazone hydrochloride ODT formulations (F1 to F10) highlighted variations in thickness, diameter, hardness, and wetting time, reflecting the impact of the formulation components. The thickness of tablet formulations (F1 to F10) ranged from  $3.72 \pm 0.24$  mm to  $4.19 \pm 0.31$  mm, and the diameter ranged from  $8.02 \pm 0.55$  mm to  $9.09 \pm 0.71$  mm. These

values fall well within the ideal pharmaceutical range (2-5 mm thickness and 6-12 mm diameter), with no significant deviation observed, confirming uniformity and suitability for orodispersible tablet design (Figure 3a). These values ensure proper handling, uniformity, and patient compliance for orodispersible tablets. The values are considered ideal for orodispersible tablets based on commonly accepted pharmaceutical manufacturing practices and patient usability standards. These dimensions ensure the tablets are easy to handle, have sufficient mechanical strength, and are comfortable for oral administration without water. Most marketed ODTs and literature-reported formulations also follow these size limits. Additionally, these ranges align with standard punch sizes used in tablet manufacturing.<sup>22</sup> Both EDC-BS formulations (F1-F4) and NBS formulations (F5-F8) exhibited comparable dimensions, with minor differences attributed to formulation composition and compression forces. Hardness values ranged between 3.85 and 5.91 kg/cm<sup>2</sup>. EDC-BS formulations (F1-F4) demonstrated higher hardness, particularly F3 (5.91 kg/cm<sup>2</sup>) and F4 (5.85 kg/cm<sup>2</sup>), which contributed to their mechanical stability (Figure 3b). NBS-based formulations (F5-F8) showed moderate hardness values, while the standard formulation (F9), containing crosspovidone, exhibited an ideal hardness of 5.89 kg/cm<sup>2</sup>, serving as a benchmark for comparison. Wetting time, a critical parameter for ODT performance, varied across formulations. EDC-BS formulations showed faster wetting times, with F3 achieving 26.34 sec, indicating its rapid disintegration potential (Figure 3c). In contrast, NBS-based formulations exhibited longer wetting times, such as F8 (65.58 sec), which could hinder their disintegration efficiency. The

standard formulation (F9) achieved an optimal wetting time of 28.47 sec, underscoring its efficiency and providing a point of reference for comparison. F3 (EDC-BS), with its balance of mechanical robustness and rapid wetting time, closely aligned with the performance of the standard formulation. In conclusion, F3 (EDC-BS) emerged as the most promising formulation, closely matching the performance of the standard crosspovidone-based formulation (F9) in terms of hardness and wetting time. This demonstrates the potential of EDC-crosslinked banana starch as a viable alternative to conventional superdisintegrants in ODTs. NBS-based formulations, while promising, require further optimization to improve wetting time and mechanical properties.

### Friability and Disintegration time

The friability and disintegration times of pioglitazone hydrochloride ODT formulations (F1 to F10) were evaluated to assess mechanical stability and rapid disintegration, key attributes for ODTs. Most formulations exhibited friability values within the acceptable limit of  $\leq 1\%$ , except for F6 ( $1.281 \pm 0.02\%$ ) and F7 ( $1.353 \pm 0.05\%$ ), which exceeded the threshold (Figure 4a). EDC-BS formulations (F1-F4) demonstrated excellent mechanical stability, with F3 ( $0.558 \pm 0.03\%$ ) and F4 ( $0.688 \pm 0.03\%$ ) showing the lowest friability values. In contrast, NBS formulations (F5-F8) exhibited variable results, with F6 and F7 showing poor mechanical strength. The standard formulations (F9 and F10) containing crosspovidone had low friability values, particularly F10 ( $0.581 \pm 0.08\%$ ), highlighting their robust mechanical properties. Disintegration times varied significantly across formulations, with F3 ( $29.24 \pm 2.35$  sec) and



**Figure 5:** *In vitro* drug release profile of pioglitazone hydrochloride from formulations F3, F4, F9, and F10 over 30 min. F3 and F9 demonstrate rapid and complete drug release within 15 min, while F4 shows slightly delayed but effective release. F10 exhibits the slowest release, highlighting differences in disintegration and dissolution rates. Error bars represent standard deviations.

**Table 7: Effect of EDC-BS and NBS on behavioural changes, Toxic effects and Mortality.**

Observation	Group A (Control)				Group B (EDC-BS @ 500 mg/kg bw)				Group C (EDC-BS @ 1000 mg/ kg bw)				Group D (EDC-BS @ 2000 mg/ kg bw)				Group E (NBS @ 2000 mg/kg bw)			
	24 hr	48 hr	72 hr	168 hr	24 hr	48 hr	72 hr	168 hr	24 hr	48 hr	72 hr	168 hr	24 hr	48 hr	72 hr	168 hr	24 hr	48 hr	72 hr	168 hr
Gross activity	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Convulsions	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Salivation	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Sense of touch and sound	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Urination	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Diarrhoea	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Mortality	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve

F4 (35.69±4.38 sec) meeting the ODT disintegration standard of ≤30 sec, demonstrating the efficacy of EDC crosslinked banana starch in promoting rapid disintegration (Figure 4b). NBS-based formulations showed prolonged disintegration times, with F5 (115.37±7.45 sec) and F8 (101.54±7.91 sec) being the slowest, indicating the need for further optimization. The standard formulations (F9 and F10) exhibited the fastest disintegration times, with F9 (28.25±5.33 sec) serving as the benchmark for ideal performance. In summary, F3 (EDC-BS) emerged as the best-performing formulation, combining excellent mechanical stability and rapid disintegration comparable to the standard formulation (F9). While NBS formulations require optimization to improve friability and disintegration times, EDC crosslinked banana starch shows promise as a superdisintegrant for ODTs, providing a viable alternative to conventional crosspovidone.

### **In vitro Drug Release of Pioglitazone Hydrochloride**

The *in vitro* drug release profiles of pioglitazone ODT formulations (F3, F4, F9, and F10) were evaluated, with F9 and F10 serving as standard formulations containing crosspovidone as the superdisintegrant (Figure 5). F3 and F9 exhibited rapid initial release, achieving over 78% drug release within 5 min, whereas F4 and F10 showed slower release at the same time point (68.23% and 63.44%, respectively). By 10 min, F3 (96.36%) and F9 (95.69%) had nearly completed drug release, outperforming F4 (89.96%) and F10 (78.14%). At 15 min, F3 (99.26%) and F9 (99.86%) achieved almost complete release, with F4 following at 95.24%. F10 showed delayed release, with only 83.38% of drug release observed. By 30 min, all formulations except F10 reached near-complete drug release. F3 (99.35%) matched the performance of F9 (99.93%), demonstrating that EDC-crosslinked banana starch in F3 provides drug release efficiency comparable to crosspovidone in F9. F4 (98.59%) also showed effective performance but at a slightly slower rate than F3 and F9. F10 demonstrated the slowest release (91.68%), highlighting its limitations compared to the other formulations. These results confirm that F3 (EDC-BS) is

comparable to the standard F9 (crosspovidone) in terms of drug release performance, while F4 (EDC-BS) outperformed F10. This demonstrates the potential of EDC-crosslinked banana starch as an efficient superdisintegrant for ODT formulations.

### **CONCLUSION**

This study successfully demonstrated the potential of EDC-Crosslinked Hydroxypropyl Banana starch (EDC-BS) as a novel superdisintegrant for pioglitazone hydrochloride Orodispersible Tablets (ODTs). Structural characterization using NMR and HRMS confirmed the effective crosslinking and chemical modifications, enhancing the physicochemical properties of banana starch. EDC-BS exhibited superior micromeritic properties, including excellent flowability, compressibility, and porosity, making it suitable for tablet formulations. The degree of swelling, water absorption capacity, and mechanical stability of EDC-BS were significantly improved compared to native banana starch, and were comparable to or exceeded the performance of crosspovidone, a conventional synthetic superdisintegrant. Formulations containing EDC-BS, particularly F3, showed optimal tablet characteristics, including appropriate hardness, low friability, rapid wetting time, and excellent disintegration efficiency. *In vitro* drug release studies revealed that F3 achieved rapid and complete drug release, comparable to the standard formulation (F9) containing crosspovidone, while outperforming other formulations. The safety and biocompatibility of EDC-BS were further confirmed through acute toxicity studies, which showed no adverse effects or mortality even at high doses. These findings establish EDC-BS as a cost-effective, biocompatible, and efficient alternative to synthetic superdisintegrants for ODT formulations. The improved performance of EDC-BS highlights its potential for broader applications in pharmaceutical formulations, paving the way for more sustainable and patient-friendly drug delivery systems. Further studies on long-term stability and scalability are recommended to validate its commercial feasibility.

## ACKNOWLEDGEMENT

The authors thank GITAM University, Visakhapatnam and Marri Laxman Reddy Institute of Pharmacy, Hyderabad for providing technical facilities and support to accomplish this research work.

## CONFLICT OF INTEREST

It is stated that neither of the authors have any competing financial interests or personal relationships that might have appeared to influence their work.

## ETHICAL STATEMENT

Animal studies were conducted as per CPCSEA norms and approved by the IAEC (Approval No.: PGP/LS/0034/2024). Acute toxicity testing followed OECD Guideline 423.

## ABBREVIATIONS

**EDC-BS:** EDC-Crosslinked Hydroxypropyl Banana starch; **ODTs:** Orally Disintegrating Tablets or Orodispersible Tablets; **EDC:** 1-Ethyl-3-(3-Dimethylaminopropyl) Carbodiimide; **NBS:** Native Banana Starch; **HRMS:** High-Resolution Mass Spectrometry; **NMR:** Nuclear Magnetic Resonance spectroscopy; **HPBS:** Hydroxypropyl Banana starch; **NHS:** N-Hydroxysuccinimide; **PVP K30:** Polyvinylpyrrolidone K30; **SEM:** Scanning Electron Microscopy.

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**Cite this article:** Metta S, Lankalapalli S. Novel EDC-Crosslinked Hydroxypropyl banana (*Musa paradisiaca*) starch as a Superdisintegrant for Enhanced Oral Delivery of Pioglitazone Hydrochloride in Orodispersible Tablets. *Indian J of Pharmaceutical Education and Research.* 2026;60(2):903-17.