RESEARCH PAPER

Quick-Acting Midazolam Films for Acute Seizures: Enhanced Emergency Delivery using Acetyl Hydrazine Starch as Superdisintegrant

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Running title: Modified starch as a superdisintegrant for ODFs

Abstract:

The goal of this study was to making an orodispersible drug delivery system suitable for dysphagia patients, this kind of patients do not cooperate with this emergency conditions, like seizures. The starch was chemically modified through chloroacetylation and hydrazinolysis to give acetyl hydrazine starch which is the novel superdisintegrant. The structural confirmation was accomplished using ^{1}H NMR, ^{13}C NMR and FTIR spectroscopy, though XRD and DSC analyses characterized the thermal behavior and crystallinity. SEM can show different morphological changes associated with native starch. The modified starch exhibited markedly improved swelling capacity and cold-water solubility. Orodispersible films (ODFs) containing midazolam as API were fabricated by solvent casting, incorporating the modified starch as a superdisintegrant. The ODFs demonstrated suitable mechanical properties, disintegration within 30 s, and >80% drug release within 1 min. These findings establish acetyl hydrazine starch as a promising new superdisintegrant for ODFs, offering significant potential in emergency drug delivery applications.

Keywords: Poly acetyl hydrazine grafted starch, Polymer modification, Superdisintegrant, Orodispersible film, Oral fast dissolving film, Anticonvulsant therapy.

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Introduction:

Oral dosage forms are the most frequent way to provide drugs since they are easy to use, convenient to the patient and they don't need to be kept sterile [1]. Though, patients are bedridden, elderly, pediatric, emetic, or have disorders of central nervous system often experience exertion for chewing or swallowing solid oral dosage forms due to fear of choking. For such individuals, oral disintegrating films (ODFs) offer the best alternative [2,3]. These films rapidly disintegrate or dissolve when put on the tip or base of the tongue and are rapidly wetted by saliva, enabling local and/or systemic drug absorption [4].

ODFs, also known as orodispersible films, are thin polymeric strips approximately the size of a postage imprint. They must be thin, flexible, easy to use and administer, and steady during manufacturing, packaging, and transportation. Additionally, they must deliver adequate taste and mouthfeel with a rapid disintegration time (up to 1 minute) [5,6]. A typical ODF consists of an active pharmaceutical ingredient along with a film-forming polymer, a plasticizer for flexibility and mechanical strength, saliva-stimulating agents, taste-masking agents, colouring agents, and other functional excipients such as surfactants and stabilizing agents. ODFs are gaining

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popularity as an alternative for patients suffering from dysphagia, which is common across all age groups. The ODFs have various advantages such as dosage accuracy, fast preparation, portability, safety, along with comfort of administration without the need for water or a spoon [7,8]. The oral disintegrating tablets leave disintegration remnants in the mouth until swallowed, whereas ODFs dissolve completely without interference [9]. Common production methods for ODFs include solvent casting [1] and hot-melt extrusion [10,11]. A ODF is typically a slim, flexible film of solitary or multilayer polymer having one or more dispersible APIs. When placed on the tongue, it is quickly by saliva hydrates it and make it disintegrate without the need for chewing or drinking [12,13]. Medication taken through the oral mucosa avoids fist-pass hepatic metabolism, proteases and low stomach pH, offering pharmacokinetic advantages [14, 15].

Midazolam, a benzodiazepine, is widely used for treating seizure emergencies, including acute repetitive seizures (ARS). Although parenteral routes (intravenous or intramuscular) are preferred for status epilepticus, non-parenteral alternatives become necessary when frequent dosing or practical constraints make injections unsuitable [16, 17, 18]. The therapeutic goal may be to prevent seizure recurrence, interrupt seizure sequences, or stop an ongoing episode [19]. In such cases, rapid administration by a caregiver, bystander, or even self-administration can be critical.

Currently available treatments for ARS and acute convulsive seizures, such as rectal or intranasal formulations, have important limitations. Rectal administration can be socially difficult and legally restricted [16], while intranasal routes may be poorly accepted, touching patient compliance [20]. Buccal film formulations of midazolam have demonstrated successful placement and ease of use, even without patient cooperation. These formulations offer favourable characteristics and overcome many problems of other non-parenteral forms.

In this context, starch emerges as a valuable biopolymer used as a pharmaceutical excipient owing to its versatility and minimum cost. However, native starch lacks suitable functional properties for use in ODFs owed to its low water solubility and swelling capability because of its semi-crystalline composition. To overcome these limitations, physical or chemical modifications are employed. Modified starch derivatives obtained via physical, chemical, or enzymatic means are widely utilized in the pharmaceutical and culinary industri es for their enhanced functionality. The hydroxyl groups in native starch are very important and can be responsible for chemical substitution to enhance desired properties [21, 22]. As compared to native starch, modified starches have shown improved disintegration and granular properties. Disintegrants are key excipients that facilitate the rapid breakdown of dosage forms in the buccal or gastrointestinal tract and are responsible for enhancing drug release instantly [23]. However, the availability of superdisintegrants is still limited, highlighting the need for more effective options.

The present study aims to develop a superdisintegrant for pharmaceutical drug delivery by chemical modification of starch produced using chloroacetyl chloride, followed by hydrazine hydrate treatment as a potential ODF film disintegrant. The modified starch was evaluated for its physicochemical properties, including crystallinity, morphology, water retention capacity (WRC), cold-water solubility (CWS) and swelling capacity. ODF formulations containing midazolam were formulated and characterized. Midazolam is selected as the model drug owing to its minimal therapeutic dose (5 mg) and are especially suited for emergency treatment of epileptic seizures.

Materials and Methods:

2.1. Materials

The components utilized in this study, chloroacetyl chloride, pyridine, and hydrazine hydrate, HPMC, cross-povidone, sodium starch glycolate, citric acid, and PEG, were provided from Loba Chemie Pvt. Ltd. (Mumbai, India). Moreover rectified spirit was obtained from the local market. Starch is purchased from Loba Chemicals Pvt Ltd. The starch, sourced from potatoes, is used for modification to have extra purity. This starch has an 80% amylose content and a molecular weight of 1.621×10^8 g/mol. Using DSC, the starch's gelatinization peak temperature was found to be 70 ^{0}C. The supplier catalogue number is 9005-25-8.

Ethical approval: All Experimental procedures used in this study were approved by the Research Ethics Committee at the Biocyte Institute of Research and Development, in Sangli, Maharashtra, India, in compliance with the Institutional Animal Care requirements of NC3Rs (ethical code: IAEC/BiRD/Sangli/2024-25/07/12 dated 12/07/2025).

2.2. Synthesis of Modified Starch

To synthesize chloroacetyl starch (as shown in Fig. 1), 10 g of starch was dispersed in 100 mL of pyridine. While stirring continuously, chloroacetyl chloride was taken 5mL and gradually added to the mixture. Further, stirring was continued for an additional two hours, after which the mixture was allowed to stand overnight. Thus, resulting mixture was then filtered and the rectified spirit was used to wash the residue and dried.

For further modification, dried 10 g of chloroacetyl starch were placed in a 50 mL flask containing rectified spirit. Then, with the continuous shaking the 10 mL of hydrazine

hydrate was added. After continuous stirring for two hours, the mixture was then filtered, again it was washed with rectified spirit, and dried. The resulting final solid residue was used for subsequent applications [24].

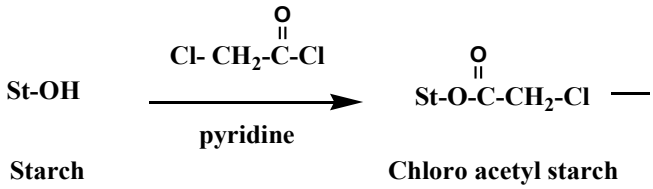

Fig.1: Synthesis of both Chloroacetyl and Acetyl hydrazine starch

2.3. Characterization

2.3.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of starch and modified starch were recorded using a THERMO NICOLOT iS50 FT-IR with Diamond ATR crystal spectrometer. The ATR crystal was directly coated with a very tiny quantity of the powdered substance, and the spectra were acquired in the 4000–400 cm^{-1} range of resolution of 4 cm^{-1}. Thirty-two scans were recorded for each sample to ensure accurate spectral data.

2.3.2. Proton and Carbon Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR)

The ^{1}H-NMR and ^{13}C-NMR spectra of starch and modified starch was developed using a BRUKER AVANCE III NMR spectrometer, which was set to operate at a frequency of 300 MHz, and deuterated water, D_2O, was utilized as the solvent for the sample, and Tetramethylsilane (TMS) was used as the internal standard. 0.5 mL of D_2O is added into the each 20mg of sample.

2.3.3. Differential Scanning Calorimetry (DSC)

A NETZSCH DSC 204 F1 DSC was used to analyzed the thermal characteristics of starch and modified starch. A nitrogen flow of 50 mL/min was used to heat 5–10 mg of each sample, sealed in aluminium pans from 40°C to 300°C at a rate of 10°C/min.

2.3.4. X-ray Diffraction (XRD)

Starch and modified starch X-ray diffraction patterns were acquired at 35 mA and 40 kV using a BRUKER AXS D8 Advance diffractometer fitted with copper Kα radiation (λ = 1.5406 Å). At a scan rate of 2°/min and step size of 0.02°, data were gathered throughout a 2θ range of 3° to 60°.

2.3.5. Scanning Electron Microscopy (SEM)

Starch and modified starch's particle form and surface morphology were examined with a JEOL JSM-6390LA scanning electron microscope running at 10 kV. In order to ensure conductivity and avoid charge collection, samples were gold-coated for five minutes.

2.4. Physicochemical Evaluation

2.4.1. Water Retention Capacity (WRC) and Cold-Water Solubility (CWS)

The aqueous suspensions of starch and modified starch were prepared by dispersing 25 g of the sample in water and stirring continuously at 30 ± 2°C for 30 minutes at a concentration of 5% w/w. Then the suspensions were centrifuged for 15 minutes. To ascertain solubility, the supernatant was transferred into the petri dish that had been weighed and dried in an oven set to 110°C until the weight remains constant. The WRC of the remaining sediment was measured by weighing it and drying it at 70°C [25]. Standard formulas were used to determine the CWS and WRC.

$$\text{CWS (\%)} = \frac{\text{Dry weight of supernatant}}{\text{Initial weight of starch}} \text{ X } 100$$

$$\text{WRC} = \frac{\text{Wet weight of sediment paste}}{\text{Dry weight of sediment paste}}$$

2.4.2. Swelling Capacity

Two grams of starch or modified starch were placed into a 50 mL graduated cylinder. The initial volume of powder was noted. After tapping the cylinder 100 times using a density apparatus, the compacted volume was noted. Water that has been deionized was added to reach the 50 mL mark. For the complete dispersion of the particles the suspension was shaken and it was kept to stand for 24 hours at 30°C. The final sedimentation volume was recorded for both samples, and swelling capacity was computed accordingly [26].

$$\text{Swelling Capacity} = \frac{\text{Swollen volume}}{\text{Initial weight of starch}}$$

2.4.3 Acute oral toxicity: In compliance with OECD guidelines, an acute oral toxicity study was conducted (OECD-423) [27]. The healthy young adult female albino rats, weighing 140 ± 10 g and between the ages of 8 and 12 weeks were selected. Before the trial of ten days, the animals were kept in a lab environment where the temperature was maintained at 22 ± 3°C and the relative humidity at 50%. The animal's room features a 12-hour artificial light and 12-hour artificial dark cycle, and unlimited laboratory food and drinking water were provided for the animals. The rats were individually marked and housed. Before dosing, the animals were fasted. The starting dosage level was chosen as 2000 mg/kg body weight, in accordance with the flow charts found in Annexure 2c. After dosing, in the first 30 minutes the animals were monitored, then periodically throughout the first 24 hours, with special care provided during the initial four hours. Daily for a total 14 days the monitoring was

continued. Individual animal record was kept, with every observation systematically documented. The variations in the animals' behavior, respiration, and circulation were recorded, along with specific changes in the skin, hair, eyes and mucous membranes, convulsions, salivation, tremors, lethargy, diarrhoea and coma. The histopathology and blood parameters were also recorded to determine any toxicity.

2.5. Formulation and Evaluation of Film

2.5.1. Preparation of Midazolam-Containing ODFs

The solvent casting method was used to formulate Oral Dispersible Films (ODFs) [28]. Take 10ml of water and add specific quantity of HPMC E5 LV (film-forming agent) and allowed to swell at an overnight. PEG 400 (plasticizer), citric acid (saliva-stimulating agent) was added to the polymer solution under continuous stirring at 300 rpm on magnetic stirrer until it can fully dissolved. Disintegrating agents such as modified starch, native starch, crospovidone, or sodium starch glycolate were then dispersed into the solution. Afterward, the drug solution (midazolam) was incorporated. The final mixture was degassed using ultrasonication at 300 W for 15 minutes and cast onto a clean, dry glass plate. The film was first let to dry for 24 hours at room temperature, and then it was dried for another 24 hours at 40°C in an oven. Once fully dried, the films were carefully peeled off and cut into 2 × 2 cm pieces. The ended films were stored between butter paper sheets, covered in aluminium foil and placed in a desiccator at room temperature.

Table 1: Formulation composition of ODFs using different disintegrants

Batches	Midazolam (mg)	HPMC E5 LV (mg)	Modified starch (mg)	Starch (mg)	Cross Povidone (mg)	Sodium starch Glycolate (mg)	Citric acid (mg)	Poly ethylene glycol (ml)	Water (ml)
F1	120	500	40	-	-	-	20	0.2	q.s.
F2	120	500	60	-	-	-	20	0.2	q.s.
F3	120	500	-	40	-	-	20	0.2	q.s.
F4	120	500	-	60	-	-	20	0.2	q.s.
F5	120	500	-	-	40	-	20	0.2	q.s.
F6	120	500	-	-	60	-	20	0.2	q.s.
F7	120	500	-	-	-	40	20	0.2	q.s.
F8	120	500	-	-	-	60	20	0.2	q.s.

2.5.2. Evaluation of Buccal Film

2.5.2.1. Preliminary Characteristics

1. **Film Forming Capacity**: This describes a polymer's capacity to produce films that are visible from the casting surface. Based on their abilities to construct films, the films were rated as extremely poor, poor, average, good, better, or best.[29]
2. **Physical Appearance**: Visual parameters are carried out to check film's appearance, parameters like Surface texture, color, uniformity, and transparency were estimated.
3. **Tackiness:** The tackiness was evaluated qualitatively by pressing the film between fingertips and the results were reported as either tacky or non-tacky.

2.5.2.2. Spectral and Morphological Characterization

1. **FTIR Interaction Study**: The determination of interactions between the drug and ODF and its components were analysed using Fourier Transform Infrared (FTIR) spectroscopy (THERMO NICOLOT iS50 spectrometer). The wavenumber range was used to scan the sample is 4000–400 cm^{-1}
2. **Surface Morphology**: Using a SEM (JEOLJSM-6390LA) the optimized film surface morphology was observed. Using a 1.0 kV excitation voltage, images were taken at various magnifications [30].

2.5.2.3. Key Formulation Characteristics

1. **Thickness:** The thickness uniformity was measured using a calibrated digital Vernier calliper, for the dose accuracy. The 10 films from each formulation were selected to measure its thickness and the average was calculated [31].
2. **Weight Variation**: The films are cut into 2 × 2 cm^2 and weigh the films individually by using electronic balance. The average weight of the three films was used to evaluate weight variation [32].
3. **Surface pH Study**: The pH of film surface was determined, to check and prevent hazard of

mucosal irritation. After coming into touch with 1ml of distilled water each film was left to swell for 3min. A combined pH electrode was gently placed on the surface for 1 minute, and the pH was recorded. Observe it for 3 times and calculate its average value [33].

4. **Folding Endurance**: The film's flexibility reflected in its folding endurance. The identical crease on each film was folded repeatedly until a crack developed. The folding endurance rating was determined by the counting the number of folds needed to explain the initial crack [34].
5. **Content Uniformity Assay:** To determine drug uniformity, cut 2 × 2 cm² films, and for 30min., each film was submerged in 10ml of distilled water and sonicated. After filtration, determine absorbance at 220nm by using UV spectrophotometer [35].
6. **In-vitro Disintegration Time**: It can be evaluated visually. Each 2 × 2 cm² film was kept at 37 ± 0.5 °C in a petri dish containing 25ml of phosphate buffer (pH 6.8). The amount of time it took to start dispersing was noted [36]. From each formulation the six films were tested and average time was recorded.
7. **In-vitro Drug Release Studies**:
   Simulated Saliva Preparation: 8g of NaCl, 0.19g of potassium phosphate monobasic and 2.38g of sodium phosphate dibasic were dissolved in 1000ml of distilled water to create simulated salivary fluid (pH6.8). A pH adjustment was made to 6.8 [37].
   Dissolution Testing: This study was conducted using simulated saliva (30ml) as the dissolving media in a beaker, kept at 37 ± 0.5 °C. The dissolving media was stirred at 100 rpm. Aliquots of 1 mL were withdrawn at time intervals of 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 minutes and replaced with fresh medium [38]. The drug content in the withdrawn samples was analysed using UV spectroscopy.

Result and Discussion:

3.1. ***Synthesis***

Melting point of acetyl hydrazine starch, starch and chloroacetyl starch were found to be 245-247°C, 258-260°C and 235-240°C, respectively, which indicates the creation of a product.

3.2. ***Characterization***

3.2.1. ***Fourier transform infrared spectroscopy***

Starch and modified starch FT-IR spectra were recorded using a THERMO NICOLOT iS50 FT-IR Spectrometer, as shown in Fig. 2. FT-IR spectroscopy is a valuable method for characterizing starch structure, its crystallinity, moisture content, and the effects of processing or modification. A very wide peak at around 3100–3600 cm^{-1} resulted hydroxyl groups (O–H) from the stretching vibration. At 2929 cm^{-1} the sharp band was corresponded to the asymmetric stretching vibration of carbon-hydrogen (-CH_2) groups. O–H bending vibrations are responsible for the typical band of absorption at 1639 cm^{-1}. C–H deformation vibrations were responsible for the absorption bands in the 1149–1339 cm^{-1} range. Between 1077 and 1149 cm^{-1} two distinctive peaks were found, and they were accredited to C–H and C–O–H bending vibrations. The anhydroglucose ring's C–O and C–C stretching vibrations were identified as the cause of the band at 1149 cm^{-1}. Starch exhibited characteristic peaks at 993 cm^{-1} (α-(1,6) glycosidic bond), 927 cm^{-1} (α-glycosidic bond), and 859 cm^{-1} (α-(1,4) glycosidic bond) [39].

The substitution can be ensues on the hydroxyl group of starch and the broad peak due to the O–H group transforms into shrink at 3284 cm^{-1}**.** A decrease in hydroxyl groups signals strength indicated a drop in the starch's hydroxyl group concentration. Alkanes bending and C-H bond stretching resulted in the observed peaks at 2928 cm^{-1} and 1360 cm^{-1}, respectively. The stretching of cyclic ether groups was responsible for the peak at 1077 cm^{-1}**.** Modified starch also exhibited characteristic peaks at 993 cm^{-1} (α-(1,6) glycosidic bond), 927 cm^{-1} (α-glycosidic bond), and 857 cm^{-1} (α-(1,4) glycosidic bond).

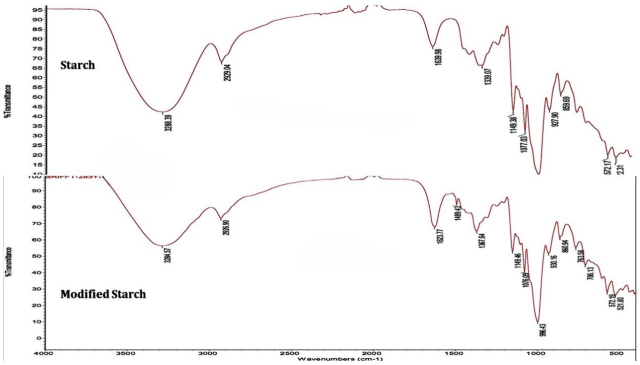

Fig. 2: Fourier transform infrared spectra of starch and modified starch.

3.2.2. ***Proton and Carbon Nuclear Magnetic Resonance***

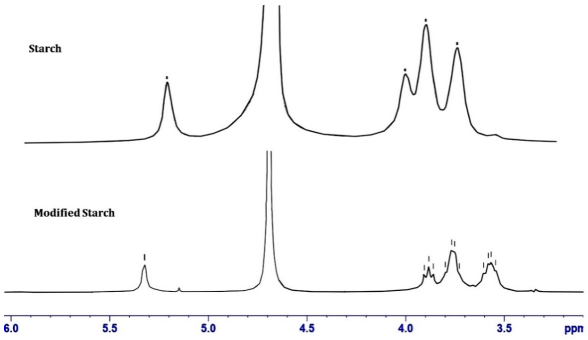

Fig.3: ^{1}HNMR *spectra of starch and modified starch.*

The effective alteration of starch into modified starch was confirmed by the ^{1}H-NMR spectra presented in Fig. 3 [40]. The protons of the anhydroglucose units in starch were observed at δ 3.5 to δ 3.8 ppm. The key peak indicating the glycosidic linkage (α-anomer) is the equatorial protons of the anhydroglucose unit, which were observed at δ 5.321 ppm. Additionally, the residual water peak appeared at δ 4.7 ppm the signal was corresponding [41,42]. In the consideration of modified starch, the protons of the anhydro-glucose units were found to be between δ 3.5 to δ 4.0 ppm as a multiplet. These multiplets are attributed to the substitution of acetyl hydrazine on the hydroxyl groups. The equatorial protons of the anhydroglucose unit in the modified starch were observed at δ 5.321 ppm, and the residual water peak remained at δ 4.7 ppm.

The ^{13}C NMR spectra of modified starch and starch are shown in Figure 4. The various carbon signals from both starch and modified starch are well resolved. The ^{13}C NMR spectra indicate that the unique carbon environments in the glucose units give rise to distinct resonances. The starch signals are broadly consistent with those reported in the literature [43,44]. The carbon signals of starch, from C1 to C6, were found in the range of 99.63 to 60.50 ppm. The C1 anomeric carbon (α-linked) was observed at 99.63 ppm. The secondary alcohol carbon C2 (CH–OH) was observed at 76.78 ppm. The secondary alcohol carbons C3 and C4 were observed at 73.33 ppm and 71.53 ppm, respectively. The peak at 71.53 ppm is attributed to the carbon near the ring oxygen (C5), while the primary alcohol carbon (C6) appeared at 60.45 ppm.

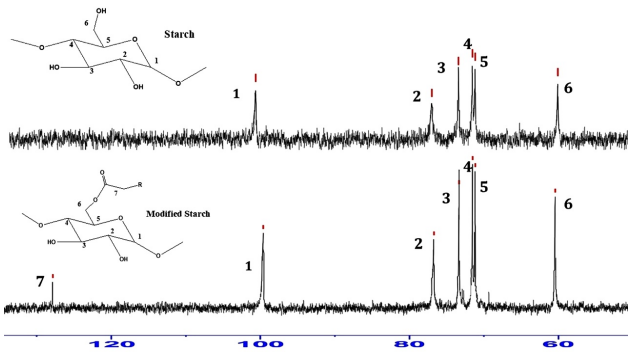

Fig.4: ^{13}C-NMR *spectra of starch and modified starch*

For the modified starch, the carbon (C1 to C6) signals were observed at 99.60 ppm (C1), 76.71 ppm (C2), 73.32 ppm (C3), 71.52 ppm (C4), 71.16 ppm (C5), and 60.85 ppm (C6). An additional signal at 127.85 ppm corresponds to the carbon of the acetyl group (C7).

3.2.3. *Differential Scanning Calorimetry (DSC)*

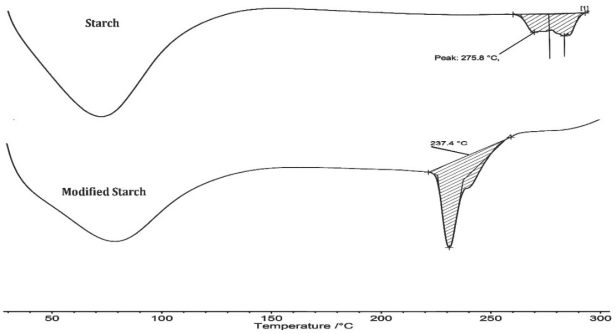

Fig. 5: DSC of starch and modified starch.

DSC are powerful technique used to analyse the thermal properties of starch. The position, shape and area of the peaks in a DSC spectrum reflect the molecular organization and interactions within the starch. These parameters allows the tailoring of starch-based materials for specific applications in food, biomaterials and pharmaceuticals. A DSC thermogram of starch, presented in Fig. 5, indicated an endothermic peak (gelatinization) at 70 °C. A second endothermic peak, observed at 275.5 °C, shows amylose–lipid complex melting or retrogradation of amylopectin during storage. At 80 °C the modified starch displayed a gelatinization peak and at 237.4 °C it displayed a second endothermic peak. These results confirm that the starch was modified and successfully transformed into acetyl hydrazine starch.

3.2.4. *X-ray diffraction (XRD)*

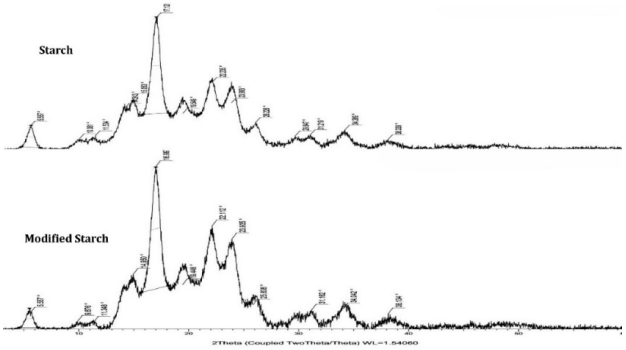

Fig.6: X-ray diffraction spectra of starch and modified starch.

The X-ray diffraction (XRD) delivers insight into the long-range arrangement of molecular, recognized as crystallinity,

which related with double helical packing [45]. As shown in Fig. 6, starch displayed diffraction peaks and diffraction peaks at 2θ values of 14.21°, 15.05°, 17.12°, 19.54°, 22.23°, and 23.99° in a typical A-type crystalline structure [46]. After starch modification, there is no any significant changes in crystallinity were observed. The diffraction peaks remained at approximately 14.95°, 16.99°, 19.44°, 22.23°, and 23.99° (2θ).

3.2.5. *Scanning Electron Microscopy (SEM)*

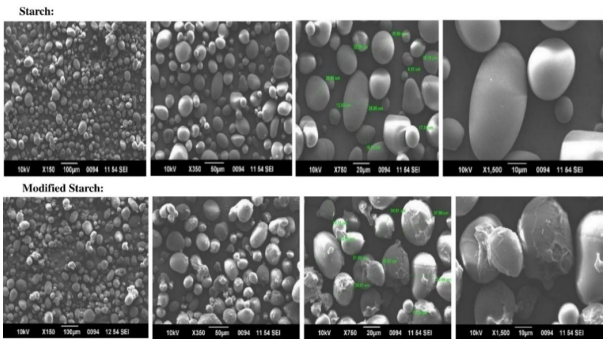

Fig.7: SEM photographs of starch & modified starch.

The scanning electron microscopy (SEM) analysis gives critical insight into starch granule morphology, which can impact on both functional applications and processing performance. The SEM photomicrographs in Fig. 7 show considerable variations in size, shape and surface morphology between modified and native starch. The native starch exhibited a smooth surface with a poly-oval structure, lacking of cracks or pores, on the other hand, the transformed granules tended to have rough, breaking surface and an irregular poly-oval shape. These changes may result from alterations in the granular structure during the modification behaviors.

3.3 Cold water solubility, water retention capacity and swelling capacity:

Figure 8 indicates the cold-water solubility, swelling capacity and water retention capacity, of native and modified starch. The existence of highly inflated starches that do not sediment under moderate centrifugal force is reflected in CWS, which shows how soluble starch molecules are [47]. In contrast, WRC and swelling power reflect starch's capacity to bind to water through hydrogen bonding [48]. The cold-water solubility of native starch was found to be 8%, while that of modified starch increased to 24%, suggesting that the modification process improved starch solubility. Similarly, the WRC increased from 1.33 g/g in native starch to 2.95 g/g in modified starch, indicating approximately a 2.2-fold increase. These changes highlight the substantial structural modifications induced by the treatment, including partial disruption of crystalline zones and hydrogen bonding networks within the starch granules.

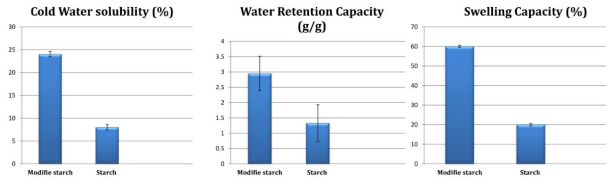

Fig.8: CWS, WRC and Swelling capacity data of modified starch & starch

While amylose functions as both a diluent and an inhibito r of swelling, specifically when lipids and proteins are pr esent, creates insoluble amylose compounds when swelling and gelatinization occurs. The swelling behavior of starch granules due to Amylopectin content [49]. In the native starch, initial volume of 0.5 cm increased to 0.6 cm after hydration, indicating a swelling capacity of 20%. In the modified starch, initial volume of 0.5 cm to 0.8 cm, representing an improved swelling capacity of 60% presented in fig 8. The increased swelling capacity observed in the modified starch can be accredited to compositional and structural alterations that arised during modification. These changes can disrupted hydrogen-bonded networks and crystalline regions, increasing the availability of hydroxyl (OH) groups and enhancing water penetrability.

Allied to the modified starch and native starch exhibited increased permeability to water, enabling improved swelling and hydration competences. This enhancement is typically attributed to chemical processes that compromise the internal structure of starch. The reduction of a firm network structure and the enhance in free functional groups such as amino groups facilitated greater water penetration into the starch granules, resulting in higher WRC, CWS and swelling capacity.

3.4 Acute Oral Toxicity: This toxicity study of modified starch was investigated according to the OECD guideline 423. Starch and its derivatives are generally considered safe for food use owing to their low or insignificant harmful effects. For the study, a dosage of 2000 mg/kg was selected based on the flow chart in Annexure 2c. The results demonstrated that modified starch has low acute toxicity, as no mortality was observed among the three animals tested at this dosage level 2000 mg/kg. The results of blood parameters also indicate that there is no harmful effect on the blood and organs.

3.5.1. Evaluation of Buccal Film:

API containing in the typical ODF, plasticizers, saliva-stimulating substances, film-
forming polymers, and other essentials such sweeteners an d superdisintegrants [50]. In the current investigation, various oral dispersible formulations were made, the type

and quantity of disintegrant varying but the other constituents remaining constant (Table 1). The solvent casting method was used to effectively prepared ODFs. The resulting ODFs had smooth surface, were colorless, translucent, flexible and were simple to remove from the mold.

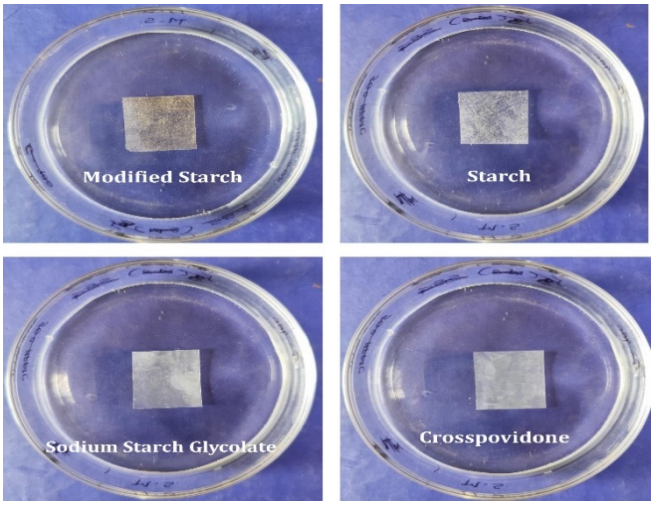

Fig.9: Photographs of Orally Disintegrating Films

3.5.2.1 Preliminary characteristics

The ODF formulation's physical and chemical characteristics were present in the Table 2. The film-forming capacity of ODFs was evaluated based on visual appearance, uniformity, ease of peeling from casting surfaces, and structural integrity. The characterized films were as poor, average, good or very good depending on their ability to form intact, uniform films without cracking or sticking excessively.

Table 2: Preliminary characteristics of the ODF formulations

Batches	Film Forming Capacity	Appearance	Tackiness
F1	Very Good	Transparent with a Yellowish tint	Non-tacky
F2	Very Good	Transparent with a Yellowish tint	Non-tacky
F3	Good	Transparent with a white tint	Non-tacky
F4	Good	Transparent with a white tint	Non-tacky
F5	Very Good	Transparent	Non-tacky
F6	Very Good	Transparent	Non-tacky
F7	Very Good	Transparent	Non-tacky
F8	Very Good	Transparent	Non-tacky

The modified starch, synthesized through chemical treatment, exhibited significantly enhanced film-forming properties, with a non-tacky and transparent appearance with a slight yellowish tint, presented in fig 9. The modification likely presented functional groups that improved polymer chain interactions and water uptake, resulting in more flexible, transparent, and smooth films. These films could be easily peeled from the casting surface, indicating sufficient mechanical integrity and cohesiveness

3.5.2.2. Spectral Characterization:

1. FT-IR interaction study:

The FT-IR spectra of the midazolam containing oral disintegrating film revealed several diagnostic peaks that make up well with the recognized vibrational bands of functional groups. Midazolam exhibited characteristic peaks at 3065 cm^{-1} (aromatic C–H stretching vibrations); at 2915 cm^{-1} and 2847 cm^{-1} (aliphatic C–H stretching vibrations); and at 1633 cm^{-1} (C=C stretching vibrations within aromatic rings). C–N stretching vibrations—indicative of amine or imine functionalities—were detected at 1427 cm^{-1} while C–H bending vibrations appeared at 1464 cm^{-1}.

No novel absorption bands or significant shifts were detected; This type variations can show chemical interactions (e.g., formation of bonds with excipients). The stability of these peak positions in the film formulation can be concluded the compatibility. Their constant presence in the FT-IR spectra observed in fig. 10 of the final film formulation strongly shows that the molecular structure remains integral and unmodified. Therefore, a formulation study midazolam oral disintegrating films assessed via FT-IR investigation found no chemical reaction between midazolam and the excipients.

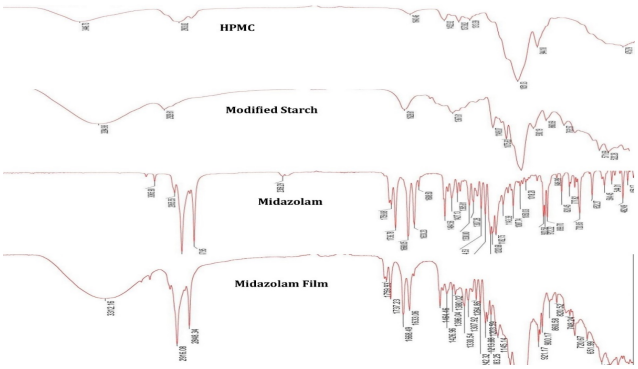

Fig.10: FT-IR spectra of midazolam, HPMC, modified starch, and Physical mixture

2. Morphological properties:

SEM provides information about microstructural and surface topography characteristics of modified starch films, which are observed in fig 11 at different µm.

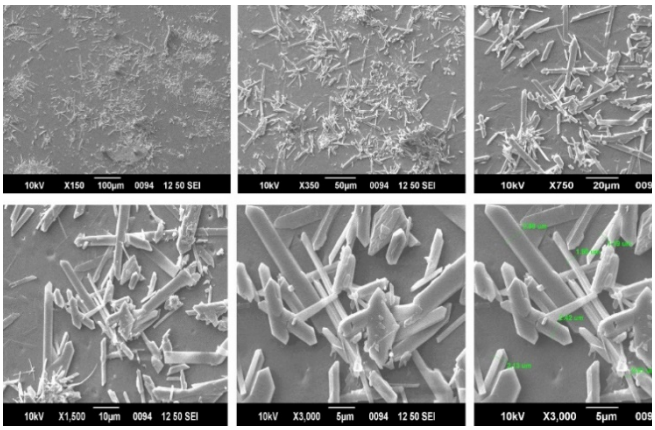

Fig.11: SEM photographs of the ODF of modified starch

The modified starch film showing discrete morphological changes like surface appeared rougher and more irregular. These variations can be attributed to the commotion of hydrogen bonding in the starch matrix owing to chemical modification. These microstructural changes are directly associated with the enhanced disintegration, swelling and drug release behavior of the film. Likewise, the irregular and rough surface may leads to rapid water uptake and drug loading capacity of the film. The enlarged surface area and free volume within the matrix makes the film more apposite for orodispersible delivery systems.

3.5.2.3. Key formulation characteristics.

1. Thickness: The film thickness will directly affect the mechanical properties such as, uniformity of drug content and disintegration. The thickness of the ODFs was noted at different points across the film surface to ensure uniformity. The film thickness was varied from 0.56 to 0.81 shown in Table 3. The uniform thickness in batches shows good control over the casting and drying processes.

2. Weight Variation: The weight variation of film, affects dose uniformity and consistency in drug delivery, and uniform weight ensures that each film contains accurate amount of drug and excipients. In this study, the weight of individual ODFs was determined by randomly selecting multiple films from each batch and weigh by using an analytical balance. The minimum weight variation in the film indicating good uniformity in film casting, spreading, and drying processes. This confirms reliable thickness, uniform drying and eventually, stable weight per unit area.

Suitable weight variation typically falls within ± 5% of the average film weight. In this study, the weight variations of films were ranging from 0.27 to 0.43, confirming the reproducibility of the manufacturing process.

Table 3: Physicochemical properties of ODFs

Batches	Thickness (mm)	Weight Variation (gm)	Surface pH	Folding endurance	Disintegration Time (sec)
F1	0.056 ± 0.27	0.030 ± 0.51	6.5 ± 0.23	201.7 ± 0.82	29.67 ± 0.45
F2	0.061 ± 0.32	0.037 ± 0.44	6.2 ± 0.19	212.7 ± 0.88	28.00 ± 0.58
F3	0.080 ± 0.59	0.040 ± 0.82	6.4 ± 0.54	105.7 ± 0.95	60.67 ± 0.65
F4	0.081 ± 0.61	0.030 ± 0.77	6.3 ± 0.58	126.0 ± 0.91	57.33 ± 0.81
F5	0.079 ± 0.42	0.037 ± 0.65	6.6 ± 0.32	213.3 ± 0.84	23.67 ± 0.32
F6	0.077 ± 0.45	0.027 ± 0.52	6.7 ± 0.38	210.3 ± 0.81	25.67 ± 0.28
F7	0.061 ± 0.39	0.033 ± 0.46	6.4 ± 0.29	208.3 ± 0.79	27.33 ± 0.36
F8	0.078 ± 0.35	0.043 ± 0.48	6.3 ± 0.35	214.7 ± 0.90	26.33 ± 0.75

3. *Surface pH study:* Surface pH parameter is used for buccal or sublingual administration of drug and the pH should be close to the physiological pH of the oral cavity as between 6.5–7.5, to reduce the risk of mucosal irritation and ensure patient relief. In the present study, the surface pH of all ODFs was observed by moistening the film with distilled water and placing the pH electrode in this solution. All the film's surface pH ranging from 6.2 to 6.7, which is within the acceptable range for oral administration.

4. *Folding endurance:* It is used to measure the mechanical strength and flexibility of film formulations; in this film can be folded at the same spot without cracking or breaking. The films were prepared by using modified starch showed higher folding endurance than the native starch, representing enhanced flexibility and tensile strength. In this study, the modified starch films shows folding endurance values ranging from the 105 to 124, representing good mechanical integrity. High folding endurance ensures that the films can be handled without tearing or crumbling, which is critical for maintaining dose integrity during storage, transportation, and administration.

5. *Content uniformity assay:* Drug content uniformity was calculated for modified starch-based films, and UV spectra are presented in Figure 12. The dose in each film unit of 2 × 2 cm^2 was estimated to be 8-10 mg. After assay using UV spectroscopy, the percentage of drug content ranged from 89.3% - 95.5%. Almost all the films had a uniform quantity of drug and met the specification, with very little difference in the content uniformity of drug.

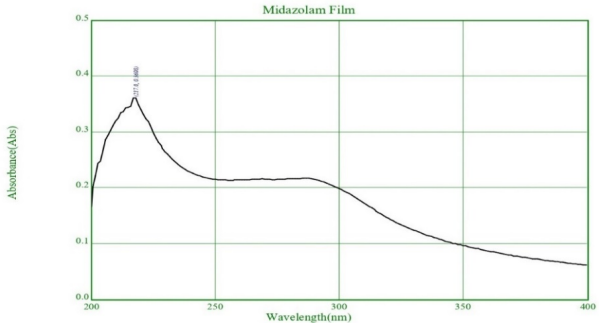

Fig.12: UV Spectra of modified starch-based midazolam ODF

6. *In-vitro disintegration of Films:* Humans have an average of less than 6 mL of saliva in the buccal cavity; therefore, the conventional instruments that are used with 900 mL media are not suitable for testing the disintegration or dissolution time of ODFs and may not represent the actual disintegration or dissolution rate in vivo. Therefore, we opted for using of Petri dish method, which is best comparable to the buccal cavity. Moreover, the absence of significant agitations and the media volume used in testing for disintegration or dissolution rate measurement are comparable to the static environment and saliva volume, respectively, in the buccal cavity [51]**.** Disintegration time is a critical quality attribute for rapid orally disintegrating films, as it determines how quickly the film dissolves or breaks apart in the oral cavity without the need for water. For effective patient compliance, especially in pediatric, geriatric, or emergency care, ODFs must disintegrate rapidly, typically within 30 to 60 seconds [23].

In-vitro method was used in this work to assess the disintegration time of ODFs. The films were placed on a petri plate moistened with simulated saliva, and the time taken for full disintegration was noted. The disintegration time in the range of 23-28 seconds, indicating rapid oral delivery. Modified starch contains functional groups that enhance matrix breakdown and water absorption, promoting faster swelling, hydration and disintegration. A shorter disintegration time ensures quicker onset of drug action and enhances patient convenience, particularly for those patients having swallowing difficulties or in situations where immediate drug delivery is required, like seizure attacks or allergic reactions.

9. In vitro release studies:

The modified starch-based ODF of midazolam was significantly reduced dissolution time as compared to films formulated using native starch. The film showed quick disintegration, rapid hydration, and rapid drug release, typically within 30–60 seconds.

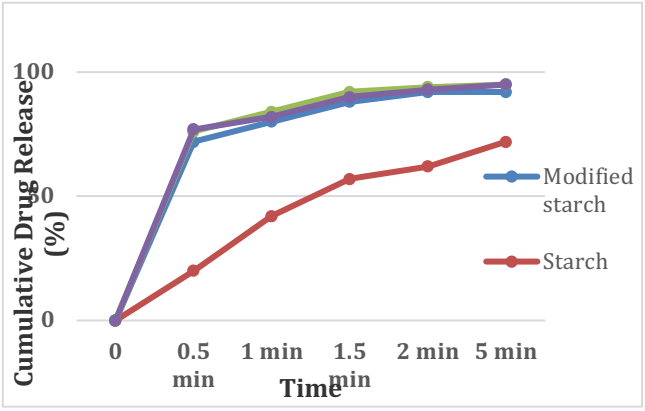

Fig.13: Release profiles of ODFs

Conclusion:

The current research confirmed the synthesis, characterization and application of chemically modified starch for the formulating of orally disintegrating films. The modification of starch with acetyl hydrazine groups were confirmed through FT-IR, ^{1}H NMR, and ^{13}C NMR analyses, which exposed discrete structural changes in the hydroxyl groups (OH) of the glucose units. Thermal analysis using DSC was confirmed the conversion of native starch to its modified form by showing altered gelatinization and melting states, while XRD patterns shows that modification did not significantly disturb crystallinity. SEM analysis supported structural alterations, with modified starch granules displaying rougher, irregular surfaces, polyhedral morphology of native starch.

The better water retention capacity (WRC), cold water solubility and swelling capacity of modified starch conventional a significant improvement in its functional qualities. These improvements can be accredited to the disruption of crystalline zones and hydrogen-bonded networks, resulting in enhanced water permeability and better hydration. Suggesting reduced oral toxicity, the LD_{50} value of modified starch was greater than 2 g/kg.

The modified starch was further explored for its use as a superdisintegrant polymer in ODF formulations. Modified starch-based films showed superior physicochemical characteristics, including smoothness, non-tackiness, transparency, good peel ability. Critical formulation parameters such as uniform thickness, acceptable surface pH, minimal weight variation and high folding endurance confirmed the mechanical integrity and reproducibility of the prepared films. Prominently, the modified starch ODFs displayed significantly enhanced swelling behavior, rapid disintegration within 28–35 seconds and uniform drug content, aligning with standards for orodispersible delivery systems. The midazolam-loaded films exhibited rapid disintegration, rapid hydration and complete drug release within 40–60 seconds.

These can be concluded that chemical modification of starch not only improves its physicochemical and functional properties but also enhances its appropriateness as a disintegrant polymer for ODFs, offering potential applications in pediatric, geriatric and emergency care where fast onset of drug action is critical.

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