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Development of Starch-based Orodispersible Films for Paracetamol Delivery: A Comparative Study

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Abstract

Orodispersible films (ODFs) have emerged as practical dosage forms due to their ease of application, dosage flexibility, and rapid disintegration in the oral mucosa without water, enabling rapid drug release. Analgesics and antipyretics are expected to have rapid effects, particularly in pediatric patients. In this study, ODFs were produced using a simple method that provides rapid drug release and doesn't require additional components like cross-linking agents. The aim of the study was to develop paracetamol-loaded starch-based films useful for children, patients experiencing vomiting, or those having difficulties. Orodispersible films were prepared *via* the solvent casting method using wheat, rice, and corn starches. The films were evaluated for their physical properties, including thickness, mass, surface pH values, swelling index, and disintegration and dissolution time. The results revealed that all films exhibited dissolution times of under 3 min, with approximately 80% of paracetamol release, demonstrating rapid and efficient drug delivery. The surface pH values were close to the pH of the oral cavity, indicating minimal risk for irritation. The characterizations of films were determined using Fourier transform infrared spectroscopy-attenuated total reflectance (FTIR-ATR), X-ray diffraction (XRD), and thermogravimetric analysis (TGA) techniques. FTIR-ATR analysis showed no differences between starch types and paracetamol was physically bound to the films. XRD patterns indicated amorphous structures resulting from starch gelatinization. TGA analysis showed rice starch films exhibited the highest weight loss and the least thermal stability. The results demonstrated synthesized ODFs can be utilized as carriers for paracetamol and could potentially be used for other active ingredients.

Keywords

orodispersible film, paracetamol, starch, drug release, solvent casting

1 Introduction

Orodispersible films (ODFs) have gained significant attention in recent years as an innovative and patient-friendly dosage form. Traditional dosage forms may not be suitable for certain patient groups, including pediatrics, geriatrics, and individuals with dysphagia or psychiatric conditions. Some individuals may struggle to take their prescribed doses due to difficulties in swallowing, while others might keep tablets under their tongues and take them off later [1]. In some cases, medicinal products containing the required dosage may not be available, and practices such as splitting tablets and opening capsules can lead to inaccurate doses and other consequences for patient safety and treatment efficacy [2]. Incorrect dosage of medication can cause serious health problems, especially in pediatric patients; for example, pediatric patients require medication dosages appropriate for their ever-increasing body weight [3]. At the same time, the method of administration and the amount of medication are also very important for the effectiveness of the medication [4, 5].

ODFs are polymeric matrices that have been developed to avoid difficulties and challenges such as swallowing or removing from the mouth, meeting many requirements for effective drug delivery platforms [2, 6]. ODFs offer certain advantages, including more effective patient compliance, dosage flexibility, and ease of application. The mucoadhesive properties of the films reduce the risk of accidental or intentional removal of medication from the mouth. Due to their mucoadhesive properties, ODFs are particularly

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beneficial for bedridden patients, those with Parkinson's disease, those suffering from mucositis, nausea, and vomiting, and those with difficulty swallowing [7, 8].

ODFs are generally composed of water-soluble polymers and can be single- or multilayer systems intended to rapidly disintegrate in the mouth before being swallowed. Their formulations typically consist of one or more polymers containing an active pharmaceutical ingredient (API), film-forming polymers, plasticizers, sweeteners, flavorings, and colorants [8, 9]. These films can be tailored by their composition and properties, such as disintegration rate, drug loading capacity, and mechanical properties. Film properties can also be modified by varying the type, amount, or grade of polymers used in film production or by varying the manufacturing conditions [10].

Polymers produced directly from biological sources or synthesized from biological building blocks are classified as biodegradable biopolymers. Biopolymers offer significant advantages in drug delivery due to their drug loading and release properties. Numerous natural, semi-natural, and synthetic polymers have been investigated for use in ODFs formulations. Natural polymers are gaining increasing interest in the pharmaceutical industry, particularly due to their safety, biocompatibility, and biodegradability [11, 12]. Starch, a natural polymer belonging to the polysaccharide group, is found abundantly in nature [11]. Starch-based biodegradable materials have gained popularity due to their affordability and low cost, non-toxicity, and widespread availability [13, 14].

Starch is widely used in many industries as an environmentally friendly material due to its biodegradability and consists of two structurally distinct α-D-glucan components: linear amylose and highly branched amylopectin [15]. Starches originated from different botanical sources have the same structural units but differ in their molecular structures and the ratio of amylose to amylopectin, which in turn affects their physical and chemical properties [15–17]. The differences in their molecular structures and interactions significantly affect the properties of the films [18]. Native starch possesses difficulties in film formation because of its non-thermoplastic nature and tends to be brittle due to strong inter- and intramolecular hydrogen bonds; however, it can be gelatinized with water and other plasticizers such as glycerol to produce a thermoplastic starch film [15, 17, 19]. Plasticizers can penetrate the starch matrix, break down intramolecular and intermolecular hydrogen bonds, and reduce molecular interactions to increase the flexibility and processability of films because of their low molecular weight and high boiling point [20]. Volatile plasticizers such as water and non-volatile plasticizers such as glycerol or sorbitol are commonly used to provide elasticity and prevent brittleness of starch-based films [19].

The most common method for producing ODFs is solvent casting, which involves dissolving or dispersing polymers, active ingredients, and additives in a suitable solvent. The resulting homogeneous viscous solution is then poured into molds and allowed to dry [21, 22]. Furthermore, the solvent casting technique makes it easier to customize dosage because films can be formed in small quantities and readily divided into smaller pieces to satisfy precise dosage requirements [21].

Paracetamol, also known as acetaminophen, is one of the most widely recognized analgesics and is often used as a first-line treatment for many chronic pain conditions. It is generally primarily a fever reducer and pain reliever, and it is considered safe for children and pregnant women when taken at prescribed doses. Paracetamol does not possess the same anti-inflammatory properties as aspirin or ibuprofen; it is an effective alternative for patients who are sensitive to aspirin [23, 24]. Paracetamol is commonly used to relieve toothache, migraine, acute back pain, and pain following surgery [25].

According to the European Medicines Agency and Supplement I Japanese Pharmacopoeia 17th Edition (Supplement I to JP17), ODFs are thin, non-sticky dosage forms designed to dissolve rapidly in the oral cavity. They have attracted considerable attention due to their promising applications as flexible and age-appropriate drug delivery systems, particularly suitable for pediatric patients [26, 27].

There is a significant need to develop drug delivery platforms that meet the needs of the specific patient groups and address swallowing difficulties. Analgesics and antipyretics are expected to be quickly effective, especially in pediatric patients. In this context, this study developed biocompatible films that rapidly disintegrate in the oral cavity. The films were loaded with paracetamol, and their release rates were investigated. Unlike many previous studies, the films in this study were produced using a simplified method and formulation without crosslinking agents or additional excipients.

2 Materials and methods

2.1 Preparation of biodegradable orodispersible films

Biodegradable ODFs were produced by the solvent casting method using three different natural starch sources: rice, corn, and wheat. Each starch type was initially dispersed in 50 mL of distilled water at varying concentrations from

2% to 5% (w/v). After the starch was completely dispersed, sorbitol was added as a plasticizer at amounts ranging from 1.5% to 9% (w/w) based on the total dry weight of the starch. The mixtures were stirred at 85–90 °C to provide gelatinization of the starch and homogenization of the film-forming solution. The homogenized viscous mixtures were poured into petri dishes and dried in a laboratory oven at 50 °C for 24 h. The virtual properties, such as homogeneity, viscosity, and pourability, during the preparation and casting of the mixtures into the molds were also observed.

Initial trials showed that formulations containing 5% (w/v) starch resulted in excessively viscous solutions, which made the solution difficult to cast properly. Additionally, sorbitol concentrations ranging from 2% to 15% (w/w) were added to obtain films with acceptable flexibility, smoothness, and handling properties. To improve the structural integrity and mechanical properties of the films, gelatin was added to the formulations at a constant rate of 2% (w/w). Gelatin was added at high temperatures with continuous stirring until it was completely dissolved. In order to compare all the properties of the films, the ratio at which a consistent viscosity and uniform film was obtained for each starch type was determined as 2% (w/v) starch, 9% (w/w) sorbitol, and 2% (w/w) gelatin.

Paracetamol was selected as a model drug for inclusion in ODFs. During the film preparation process, 250 mg of paracetamol was added to each formulation, regardless of the type or the starch used. The amount of paracetamol was determined so that 40 mg of paracetamol was added to each 2 × 2 cm (4 cm^2) film section used for drug release. This dosage was added equally to all the films to allow comparison of release profiles in every film formulation.

2.2 Properties of orodispersible films

2.2.1 Thickness and mass measurements

The thickness and weight of the ODFs were measured to assess the homogeneity and consistency of the formulations. The thickness of the films from each formulation was measured at five different points (four corners and the center) using a digital caliper. The weights of the selected films were also determined using an analytical balance.

2.2.2 Moisture content

Moisture contents of the films were determined using a moisture analyzer (Mettler Toledo). Film samples weighing at least 0.5 g were placed in the analyzer and quickly heated to 105 °C. Heating continued until the weight change was less than 1 mg, indicating stability. The moisture contents were calculated based on the weight loss. For each starch-based film, five separate measurements were performed, and the mean values were reported [28].

2.2.3 Surface pH

The surface pH values were determined to determine the compatibility of the films with the oral mucosa. 0.5 mL of distilled water was dropped onto the surface of each film sample, and after waiting for 30 s, the surface pH was measured using a calibrated digital pH meter. The measurements were repeated 3 times for each formulation, and the average values were reported [29, 30].

2.2.4 Swelling index

The swelling behaviors of the films were determined to understand their water absorption capacity. Each film sample (2 × 2 cm) was dried in a laboratory oven, weighed, and then immersed in 20 mL of distilled water at room temperature. At certain time intervals, the films were removed from the water, the surface water was gently wiped off, and the films were weighed again. The swelling index was calculated by dividing the difference between the final and initial weights of the films by the initial weights of the films [31].

2.2.5 Disintegration time

The disintegration time is defined as the time required for the film to visibly perforate or break down when exposed to an aqueous medium. The disintegration times of the films were determined as the time required for holes to form by adding distilled water to the films [32].

2.2.6 Drug release

The drug release profiles of the paracetamol-loaded films were determined for each film. Film samples (3 × 2 cm) were immersed in a 900 mL deionized water (pH: 7) maintained at 37 °C as dissolution medium. At predetermined time intervals (1, 3, 5, 10, 15, and 30 min), 5 mL aliquots were withdrawn and immediately replaced with an equal volume of fresh medium. The amount of paracetamol released into the medium was quantified using a UV–Visible spectrophotometer (λ = 243 nm). Absorbance values were used to calculate drug concentrations at each time interval from the calibration curve [33].

2.3 Characterization of orodispersible films

Thermal methods such as thermogravimetric analysis (TGA) and other analytical methods such as powder X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FTIR) are techniques frequently used for compatibility screening of API studies [34].

2.3.1 Fourier transform infrared spectroscopy

The chemical interactions and functional groups present in the paracetamol-loaded films were analyzed using FTIR equipped with an attenuated total reflectance (ATR) accessory. Spectra were collected in the range of 4000–650 cm^{-1} with a spectral resolution of 4 cm^{-1}. This technique was used to evaluate potential interactions between the API and film-forming polymers, as well as to confirm the presence of characteristic functional groups.

2.3.2 Thermogravimetric analysis

The thermal stability and degradation behavior of the films were evaluated using TGA. Samples were heated from 30 °C to 550 °C at a constant rate of 10 °C min^{-1} under a continuous nitrogen purge. The weight loss profiles were recorded to identify degradation steps and moisture content.

2.3.3 X-ray diffraction

The phase structures of the film formulations were analyzed using XRD. The measurements were carried out with a diffractometer set to 40 kV and 15 mA with Cu-Kα radiation over a scanning range of 5° to 70° (2θ).

3 Results

3.1 Visual appearance of films

The visual properties of ODFs produced in this study were evaluated for homogeneity, integrity, and pourability, since these aspects are essential for both patient acceptability and manufacturing feasibility. The images of the films are shown in Fig. 1.

The images clearly show that the transparency and structural integrity of the films vary depending on the type of starch used. Corn starch film exhibits a smooth, distinct, and uniform translucent structure. Rice starch film exhibits more remarkable transparency and integrity than corn starch film. Wheat starch film, on the other hand, exhibits properties intermediate between those of corn and rice starch films.

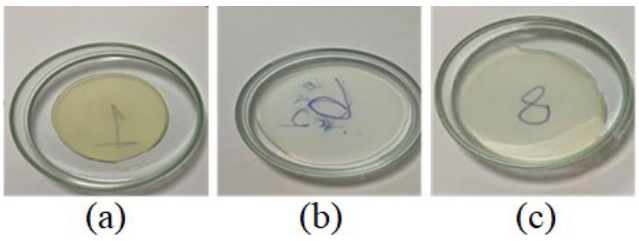

Fig. 1 Images of the films: (a) corn starch; (b) rice starch; (c) wheat starch

3.2 Thickness and mass of films

The physical characteristics of the ODFs, specifically thickness and weight, were evaluated to determine their uniformity and suitability for oral drug delivery. The thickness values and their standard deviations for films formulated with rice, wheat, and corn starches are given in Table 1.

The thickness values of up to 0.35 mm for films with a size of 2 × 3 cm are considered acceptable [35]. The thickness values of all films ranged from 0.14 mm to 0.17 mm, and the average thickness was found to be 0.16 mm. The thickness values of the films were found to be within the acceptable range, and the low standard deviation values indicate high reproducibility. Table 2 shows the mass values and their standard deviations of the films.

Weight and thickness consistency are important in the development of ODFs since they have a direct effect on patient safety and dose accuracy. These measurements are important indicators of manufacturing consistency and content uniformity. The optimal properties of ODFs include minimum changes in thickness and weight. All the weights of the film weights ranged from 0.69 to 0.72 g, and low standard deviation values indicate that the films are very consistent with each other [36].

3.3 Moisture content of the films

The moisture content value is an indicative parameter related to the total volume of water molecules occupied in

Table 1 The thickness values and standard deviations of the films

Rice starch films (mm)	Wheat starch films (mm)	Corn starch films (mm)
0.16	0.16	0.17
0.17	0.17	0.17
0.14	0.15	0.18
0.14	0.15	0.15
0.17	0.17	0.14
0.16^{av}	0.16^{av}	0.16^{av}
0.015^{*}	0.01^{*}	0.016^{*}

*: Standart deviation; av: average value

Table 2 The mass values and standard deviations of the films

Rice starch films (mg)	Wheat starch films (mg)	Corn starch films (mg)
0.68	0.71	0.71
0.68	0.72	0.7
0.72	0.69	0.7
0.71	0.67	0.68
0.71	0.68	0.69
0.71^{av}	0.68^{av}	0.69^{av}
0.018^{*}	0.02^{*}	0.01^{*}

*: Standart deviation; av: average value

the microstructure network of the film [37]. High moisture content in ODFs is generally undesirable because it facilitates microbial growth and causes instability of the API. Most commercial ODFs have moisture contents below 10% and often less than 5% [38]. The moisture contents of the films produced in this study using different types of starch are given in Table 3.

The average moisture contents of rice, wheat, and corn starch films were 4.4%, 4.5%, and 4.3%, respectively. While starch-based films are expected to have high moisture content due to the hydrophilic nature of starch-based polymers, all film formulations were found to have low moisture contents and were within acceptable limits.

3.4 Surface pH values of the films

Surface pH is another important parameter among the properties of the ODFs. Ideally, the surface pH of the films should be close to the pH of the oral cavity, which is approximately 6.8 [32]. Table 4 presents the surface pH values of films produced using rice, wheat, and corn starch.

The average surface pH for rice starch films was measured as 6.34, while that for wheat and corn starch films was 6.42. The surface pH values of all films were found to be close to the pH of the oral cavity. These values reduce the risk of oral irritation and provide a more comfortable user experience. The surface pH values of the films developed in this study are important for physiological compatibility and patient comfort.

Table 3 The moisture contents and standard deviations of the films

Rice starch films (%)	Wheat starch films (%)	Corn starch films (%)
4.5	4.6	4.2
4.5	4.7	4.3
4.5	4.4	4.5
4.3	4.4	4.3
4.2	4.3	4.2
4.4^{av}	4.5^{av}	4.3^{av}
0.14^{*}	0.16^{*}	0.12^{*}

*: Standart deviation; av: average value

Table 4 The surface pH values and standard deviations of the films

Rice starch films	Wheat starch films	Corn starch films
6.3	6.6	6.5
6.4	6.5	6.2
6.2	6.3	6.4
6.5	6.4	6.5
6.3	6.3	6.5
6.3^{av}	6.4^{av}	6.4^{av}
0.11^{*}	0.13^{*}	0.13^{*}

*: Standart deviation; av: average value

3.5 Disintegration time of the films

Disintegration time provides a helpful sign for the beginning of the effect of the active ingredient [39]. Disintegration time is an essential measurement for ODF innovation and evaluation because it is closely related to disintegration behaviors that facilitate rapid dissolution. However, there are not yet specific quality control standards for ODFs in the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.) [38]. For orally disintegrating tablets (ODT), the disintegration time should be between 30 s and 3 min, which is necessary for water to penetrate through capillary action [35]. The disintegration times of the films produced in this study are presented in Table 5.

Disintegration time for starch-based ODFs were found to range from 136 to 144 s, which is within acceptable limits for orodispersible dosage forms. Among the three formulations, corn starch films exhibited the shortest mean disintegration time (137.6 s), followed by rice starch (138.8 s) and wheat starch (140.2 s). The measured disintegration times coincide with the criteria specified for ODT, supporting the suitability of these films for use in rapid-onset drug delivery systems.

3.6 Swelling index of the films

Swelling is initiated by water uptake into the film matrix and is a key factor promoting adhesion of orally disintegrating films to the buccal mucosa. This hydration process not only enhances mucoadhesion but also significantly influences the release kinetics of the incorporated drug. A strong correlation exists between water uptake and drug dissolution; as water penetrates into the polymeric network, it initiates matrix expansion, facilitating the release of the API [40]. The swelling index values of ODFs formulated with different starch types are given in Fig. 2.

All starch-based ODFs exhibited a gradual increase in swelling index over the 4 min evaluation period. Among the

Table 5 Disintegration times and standard deviations of the films

Rice starch films (s)	Wheat starch films (s)	Corn starch films (s)
143	140	140
136	144	138
137	140	136
138	143	138
140	144	136
138.8^{av}	142.2^{av}	136^{av}
2.77^{*}	2.05^{*}	1.67^{*}

*: Standart deviation; av: average value

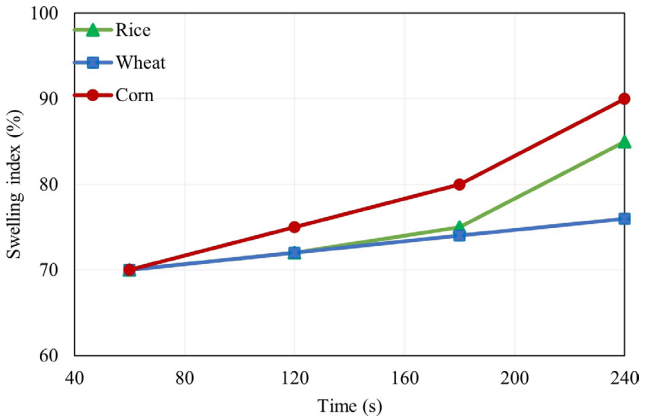

Fig. 2 Swelling index of the films

formulations, corn starch films showed the highest swelling index, reaching approximately 90%, followed by rice starch films at 85%, while wheat starch films exhibited the lowest swelling, with a maximum of 76%. These differences in swelling behavior are of practical importance as they affect the rate and extent of drug release. Swelling facilitates matrix hydration, expansion, and disintegration upon contact with saliva, enabling the diffusion of the API [41]. A higher swelling index is therefore considered advantageous, as it promotes the penetration of aqueous media into the polymeric matrix and enhances API diffusion and release kinetics [42]. The results suggest that corn starch may be particularly well-suited for formulations requiring rapid hydration and release.

3.7 Drug release

Drug release from ODFs is an important aspect that directly affects their bioavailability and therapeutic efficacy after administration [29]. Fig. 3 represents the cumulative drug release profiles of paracetamol over 30 min from ODFs formulated with rice, wheat, and corn starches.

According to the Food and Drug Adminstration (FDA), the dissolution criterion for immediate-release solid oral drug products containing a highly soluble drug substance is 80% in 30 min [43]. Paracetamol is a high solubility compound classified as a Biopharmaceutics Classification System Class I compound [44]. In the present study, paracetamol-loaded starch-based ODFs demonstrated rapid drug release, achieving 80% dissolution within the first 5 min and complete release within 30 min in all formulations, meeting FDA criteria.

All formulations showed a rapid initial drug release, with more than 90% of the drug released within the first 10 min. Corn starch films exhibited the fastest drug release, achieving almost complete drug release (97.3%) within 10 min. Rice and wheat starch films also showed efficient release exceeding 92% in the same time duration. The slightly faster release observed in corn starch films can be attributed to the higher swelling capacity, which enhances matrix hydration and facilitates drug diffusion.

These results indicate a burst release of the drug in the first minutes of the experiments, indicating diffusion of the soluble portion of the drug into the medium as soon as it comes into contact with saliva. The release profile follows exponential growth kinetics (fit curve), confirming that drug release is governed by diffusion according to the Fickian model. Fickian diffusion refers to the high-speed diffusion of the solvent into the matrix, resulting in high drug dissolution and diffusion [45]. This rapid release is particularly useful for conditions requiring immediate therapeutic action, such as pain or fever.

Kinetic model parameters were calculated from the drug release data for ODFs formulated with different starch types and given in Table 6.

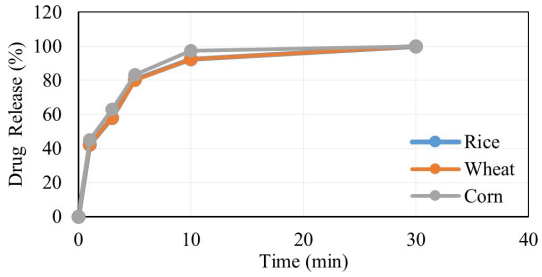

Fig. 3 Paracetamol release profile of the films

Table 6 Kinetic parameters for starch based orodispersible films*

Starch type	Zero-order		First-order		Higuchi		Krosmeyer-Peppas		
	k_0	R^2	k_1	R^2	k_H	R^2	k_P	n	R^2
Rice	2.36	0.51	0.38	0.97	23.71	0.8	41.8	0.36	0.98
Wheat	2.36	0.51	0.38	0.97	23.71	0.8	41.8	0.36	0.98
Corn	2.28	0.46	0.42	0.97	24.41	0.75	45	0.34	0.99

* k_0, k_1, k_H, k_P are the rate constants; n is the release exponent; R^2 is the coefficient of determination.

Paracetamol release profiles from starch-based ODFs were further analyzed using various kinetic models. Among these, the Korsmeyer-Peppas model provided the best fit, with high R^2 values for all starch types. The calculated n values lower than 0.45 also proved the theory derived from the release profile, indicating that the drug release mechanism predominantly follows Fickian diffusion.

To assess the similarity between the drug release profiles of different starch-based ODFs, the similarity factor of the films (f_2) were calculated. f_2 values between 50 and 100 indicate that the two dissolution profiles are similar (Table 7).

The similarity factor exhibited that the rice and wheat starch films were nearly identical profiles. Although minor differences were observed between the corn-based films and the other films, the formulations were found to have similar drug release behavior.

3.8 Fourier transform infrared attenuated total reflectance spectroscopy

Fig. 4 represents the FTIR-ATR spectra of the films prepared with wheat, rice, and corn starch.

The FTIR spectra of the starch-based ODFs exhibited characteristic functional group vibrations corresponding to the film components. Among the different starch types, remarkable variations were not observed in the characteristic region between 1500 and 400 cm^{-1} of the starch types [46]. Broad O–H stretching vibration bands were observed between 3000 and 3300 cm^{-1}, which are typical of hydroxyl groups and indicate extensive hydrogen bonding within the matrix. Additionally, O–H bending vibrations attributable to tightly bound water molecules were detected at 1650 cm^{-1} [47]. CH_2 stretching vibrations were observed around 3100 cm^{-1} [46].

Table 7 Similarity factors for starch based ODFs

Comparison	f_2 value
Rice *vs*. wheat	99.99
Rice *vs*. corn	72.81
Wheat *vs*. corn	72.67

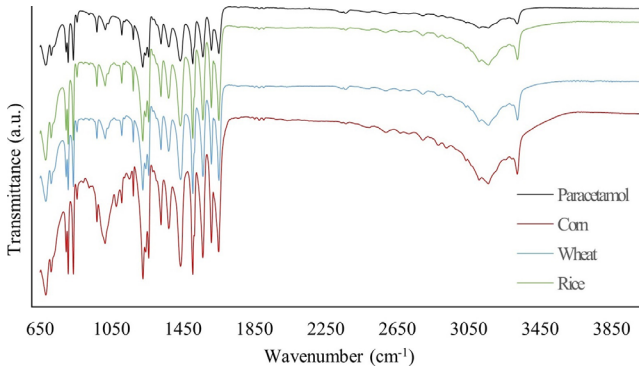

Fig. 4 FTIR spectra of the films

In the fingerprint region (1800–800 cm^{-1}), the spectra display numerous overlapping and poorly resolved peaks consistent with the complex nature of polymeric film systems [48]. C=O stretching vibrations were observed at 1653 cm^{-1} and 1562 cm^{-1}. In particular, C=C aromatic stretching bands appeared in the 1600–1400 cm^{-1} region originated from paracetamol, while highly coupled C–O and C–C vibrations, which are sensitive to the conformational and crystalline order of starch, are observed between 1300 and 800 cm^{-1}. The prominent absorption bands observed at 1155, 1125, and 1105 cm^{-1} are attributed to C–O and C–C stretching modes with contributions from C–OH vibrations, while the bands at 1080, 1047, 1022, 995, and 928 cm^{-1} correspond to C–OH bending and CH_2-related vibrations. Furthermore, distinct C–H deformation bands observed at 682 cm^{-1} [49, 50].

The main bands observed in the spectrum of paracetamol were C=C stretchings originated from aromatic benzene ring at 1140 cm^{-1}, C=O stretchings at 1560 cm^{-1} and =C–H bonds at 680 cm^{-1}. Absorption bands between 850–600 cm^{-1} indicated alkene double bonds and aromatic C–C bonds [49].

The FTIR spectra were found to be nearly identical across all starch types (wheat, rice, and corn), indicating that the use of different botanical starch origins did not significantly alter the molecular structure of the films. Importantly, the absence of new peaks or significant peak shifts in any formulation supports the conclusion that no strong chemical interactions occurred between starch types, paracetamol, and other excipients. This confirms that the films are physical mixtures rather than chemically bonded systems, which is a desirable feature in ODFs. Such non-interacting matrices facilitate the rapid and efficient release of the active substance upon administration [41].

3.9 Thermogravimetric analysis

The TGA of the ODFs prepared with corn, rice, and wheat starches are presented in Fig. 5.

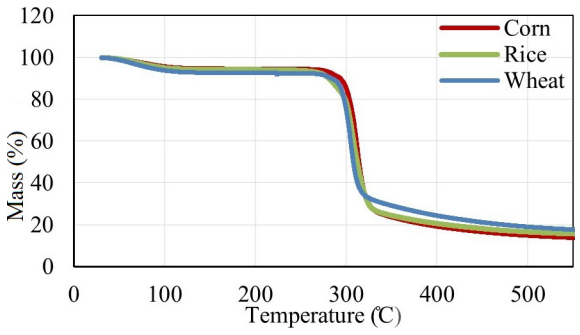

Fig. 5 TG analysis of the different types of starches

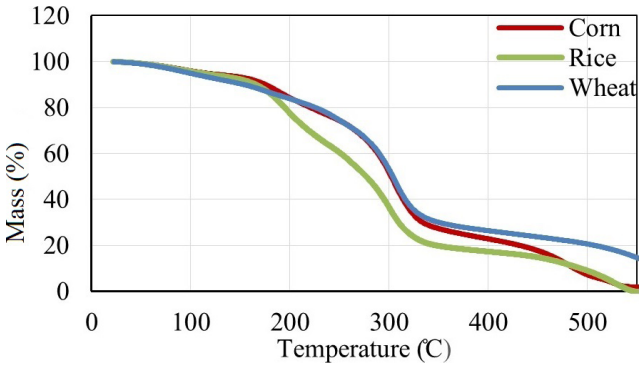

Fig. 6 TG analysis of the films

TGA of starches revealed very similar degrading behavior in the same temperature ranges. At temperatures above 300 °C, mass loss in corn and rice starches is slightly lower than in wheat starch. The TGA of the ODFs prepared with corn, rice, and wheat starches are presented in Fig. 6.

Thermal decomposition of starch generally occurs in three distinct stages. The first stage involves physical dehydration, where the amount of water lost depends on both absorbed and bound water present in the starch. The second stage involves chemical dehydration and the onset of thermal degradation. Around 300 °C, thermal reactions begin with the condensation of hydroxyl groups along the starch chains, leading to the formation of ether bonds and the release of water and other small molecules. As the temperature continues to increase, aromatic structures such as substituted benzene and furan rings are linked. In the final stage, occurring above 500 °C, carbonization reactions predominate. Aromatic carbon signals intensify, while aliphatic carbon signals decrease, indicating the formation of increasingly conjugated aromatic systems [51].

Films produced from different starches exhibited similar thermal behavior with some differences over the same temperature range. Among the films tested, rice starch films exhibited earlier onset of degradation and lower thermal stability, while wheat starch films exhibited a slightly delayed onset and a wider degradation range, demonstrating higher resistance to thermal decomposition. In the thermal region above 500 °C, approximately 20% solids residue remained in the wheat starch film, demonstrating higher thermal resistance.

3.10 X-ray diffraction analysis

Wheat, corn, and rice starches were used for the production of ODFs. XRD analysis of the starch types are given in Fig. 7.

Starch types showed similar patterns, and starches were determined to have type A crystal structure. The most

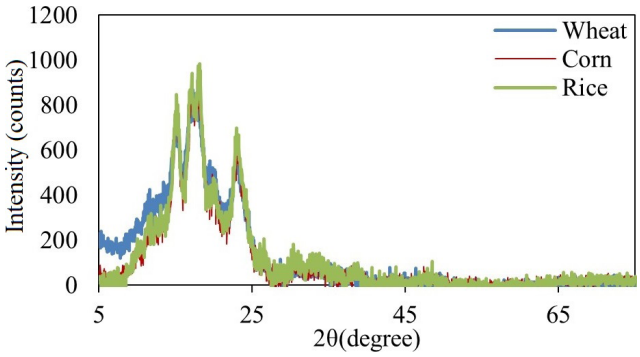

Fig. 7 X-ray diffractograms of the starches

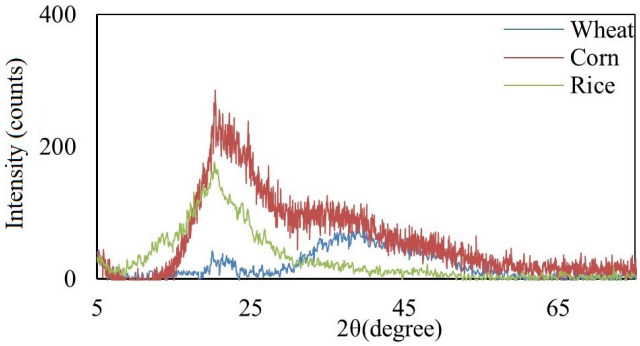

Fig. 8 X-ray diffractograms of the films

prominent peaks were observed around 2θ of 17.68°, and a few smaller peaks were observed around 5°, 11.2°, 15.16°, 19.76°, 22.96°, 26.12°, 30.88°, and 33.56° (2θ) [52]. Fig. 8 illustrates the XRD patterns of ODFs prepared with wheat, corn, and rice starch.

The structures of the films were found to be different from the original starches, with the observed peaks decreasing in intensity significantly, but no new peaks appeared. The diffractograms revealed broad, diffuse halos instead of sharp, well-defined peaks, indicating that all film samples exhibited predominantly amorphous properties. Corn starch films had a wider protrusion, while rice and wheat starch films exhibited lower density and wider protrusions. The structural changes in the starch films can be explained by gelatinization. When water penetrates the starch at the gelatinization temperature, intermolecular interactions are reduced, resulting in a more disordered structure and disruption of the crystalline structure [53].

4 Conclusion

Starch is used in the pharmaceutical industry, bioplastics, and the food industry due to its cost-effectiveness, abundance, and biocompatibility. In this study, different types of starch were investigated in the formulation of ODFs that offer significant advantages for patients with swallowing difficulties, such as pediatric, geriatric, or disabled populations.

The films were evaluated for their essential properties for orodispersible film applications. The thickness and mass values critical for uniform dosing were consistent for all films. Surface pH values were found to be close to the pH of the oral cavity, indicating compatibility with the buccal mucosa and a low risk for irritation. Among the key indicators, disintegration time is considered to be critical for ODF functionality. All film formulations demonstrated disintegration times under 3 min, consistent with regulatory expectations. Dissolution tests demonstrated rapid and effective drug release, with all films meeting FDA criteria for fast-release formulations.

A strong correlation was observed between the swelling behavior of the films and drug release rates. The corn starch films with the highest swelling index and the shortest disintegration time also showed the fastest drug release within 10 min (97.3%). The results indicate that the swelling index can be a predictive indicator of drug release behavior and allow for preliminary assessment of release performance without direct dissolution testing.

Moisture content measurements from both the moisture analyzer and TG analysis showed consistent results, confirming low moisture values for all film types. The low moisture content observed in all formulations provides advantages in terms of physical stability and extended shelf life.

FTIR-ATR spectra of the films revealed that the use of different starch types did not cause significant changes. Characteristic peaks of paracetamol remained consistent across all formulations, and paracetamol was bound physically to the films. XRD analyses confirmed that paracetamol was incorporated in an amorphous form, with no detectable crystalline peaks or new chemical bonds. The highest amorphicity was observed for the corn starch film. This film also has the highest drug release rate. The results were found to be compatible with each other; the highest amorphicity resulted in the highest swelling ratio and the drug release rate. It is believed that the gelatinization process achieved by increasing the temperature during film production disrupts the native crystalline structure of starch, resulting in amorphous film matrices.

The results obtained from this study demonstrate that starch-based ODFs are promising carriers for paracetamol and potentially other APIs. Thanks to their natural origin, biocompatibility, and rapid disintegration time, these films offer safe and effective alternatives to oral drug administration. Furthermore, rice and corn starch films performed similarly to wheat starch-based formulations, indicating that gluten-free starch sources can be effectively used in ODF production and may offer a safe alternative for individuals with gluten sensitivity or food allergies. In future studies, the potential applications of the developed films as drug delivery systems for various groups of APIs will be investigated and the effects of storage conditions on long-term structural stability will be considered.

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