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RESEARCH ARTICLE

# Engineering pH-Dependent Orally Disintegrating Tablets for Modified Indomethacin Release: A Polymer-Based Approach

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## Abstract

The application of pH-sensitive polymers has been widely explored in pharmaceutical industry because of their versatile properties. This work aims to delay the release of indomethacin (IND), a commonly used anti-inflammatory drug, using a pH-dependent polymer within orally disintegrating tablets (ODTs) and to investigate the effect of the polymer particle size on the ODTs. When developing delayed-release formulations for orally disintegrating tablets (ODTs), it's essential to balance the pellet's matrix properties to maintain integrity and delayed release. Different sizes of Eudragit L100 were used to create IND-containing pellets via extrusion spheronization, which were then embedded into the matrix of ODTs. The particle sizes displayed good elastic properties with low Young's modulus (YM) values, and there was no significant difference between the different sizes (45, 60, 93 µm; $p > 0.05$). The tensile strength of the pellets was directly proportional to YM ($p < 0.05$), providing enough support to maintain their integrity under compression. Pellets made from 63 µm Eudragit L100 had a suitable balance of mechanical and pharmaceutical properties compared to other sizes. 63 µm pellets had an aspect ratio of $1.49 \pm 0.26$ and 61% yield, while their ODTs showed a fast disintegration time of $14 \pm 0.6$ s, while modifying the drug release. Furthermore, IND exhibited modified release in acidic media (pH 1.2) and immediate release in buffer media (pH 6.8). Overall, protecting pellet integrity was crucial to delay release in acidic media and enable immediate release in alkaline media. The newly developed formulation will improve compliance and reduce side effects associated with IND and other irritant drugs particularly in elderly populations.

**Keywords** Eudragit L100 · Delayed release · Indomethacin · Orally disintegrating tablets · Pellets · PH-dependent polymers

## Introduction

Indomethacin (IND) is a commonly used Nonsteroidal anti-inflammatory drug (NSAIDs) for the management of pain, caused by arthritis and gout, particularly for elderly patients [1–3]. NSAIDs is the most widely prescribed medication with around 70 million prescriptions in the USA and 20 million prescriptions in the UK [4, 5]. However, NSAIDs can cause mucosal and gastric irritation, especially in elderly patients, which limits its clinical use [6]. The long-term use of conventional NSAIDs dosage forms was associated with local gastric irritation, leading to severe mucosal bleeding [7]. It is well documented that around 20- 30% of NSAIDs users suffer from peptic ulcers [8–11]. These side effects are attributed to the immediate release of the NSAIDs in the stomach [12]. Therefore, developing a strategy using pH-dependent polymers that delay NSAIDs release to bypass the stomach is important to minimize gastric disturbance. Furthermore, the use of orally disintegrating tablets for elderly patients is favourable, particularly for those suffering from dysphagia. Therefore, there is a need of designing a new orally disintegrating tablets with modified release capabilities. This approach will boost the patients ' compliance by easing ingestion and reducing dosing frequency [13]. Manufacturing a multiparticulate system that can be embedded

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within the matrix of an ODT was investigated in this study to achieve this goal.

Among the multiparticulates are pellets, which range in size from 0.5 mm to 2 mm with spherical shapes [14]. The drug particles are embedded within the polymeric matrices of the pellets as the API. Other excipients within the pellet's matrix are included such as flavours, binders, and plasticizers to achieve the required properties [14]. Pellets can be delivered in various forms; for instance, they can be filled in capsules or administered as a tablet when compressed. Avoiding dose dumping is another advantage of using pellets, thereby reducing the local discomfort of the sudden release of the API and supplying the medication to its site of action in the gastrointestinal tract [15]. The scale of the pellets and their bulk composition give more advantages in reducing the pace of intestinal transit and the period for gastric [14, 15].

Furthermore, the mechanical attributes associated with the pellets such as strong mechanical strength, ease of flow, reduced friability and standard packaging offer additional benefits to utilize the pellets in manufacturing various pharmaceutical formulations in comparison with others [16, 17].

Various techniques were reported for the development of pellets including extrusion spheronization, hot-melt extrusion, solution/suspension, and dry powder layering. Due to ease of use, high yield, and narrow particle size distribution, extrusion spheronization is the preferred method [18]. The technique involves agglomeration of dry powder with the help of liquid binder. Then, an extruder is used to produce a high density extrudates that converts to pellets with the help of spheronizer.

As part of the manufacturing process, various formulation parameters are required to be controlled for optimal pellet performance. For example, the surface of the pellet is necessary to be equally uniform when preparing tablets or filling capsules with pellets. Hence, the surface roughness of pellets increases the friction between these pellets and further reduces the flow rate [19]. These surface properties of roughness or fissures indirectly produce interlocking pellets, enabling their agglomeration and may form coarse particles. As a result, formulation defects could occur during compression of the pellets, reflecting on drug release properties [20]. This can lead to a significant challenge which is damaging the integrity of the multiparticulate system during the compression process to prepare the ODT. Furthermore, the extrusion spheronization speed and the duration of the preparation approach can also determine the surface roughness. The extrusion process aids in smoother surfaces of extrudates [21].

During pellet development, the first step is particle aggregation. The particle size of employed materials is considered a significant factor in determining pellet quality, shape, yield, surface homogeneity and ability to modify drug release [21]. Therefore, in the first part of this work, we aimed to prepare pellets based on a monolithic system using different particle sizes of Eudragit L100 (45, 63, 90 µm). Eudragit L100 will provide a matrix within the monolithic system and the model drug (IND) will diffuse through the matrix in a controlled manner.

Eudragits are smart synthetic polymers that consist of specific ratios of methacrylic acid, methyl methacrylate, and dimethyl aminoethyl methacrylate [22]. Eudragit polymers are applicable in modified release formulations depending on the thermoplastic and physical properties of Eudragits to modify the drug release [23]. Other uses of Eudragits include minimizing environmental impacts on drug stability, e.g., light and moisture and masking the unpleasant drug taste [23].

Properties of Eudragit L100 as a anionic copolymer include stable methacrylate, pH-dependent (soluble at $pH \geq 6.8$) and good mechanical properties rendering it suitable for delayed-release and enteric-coated dosage forms to achieve intestinal drug release at pH 6.6–7.5 [24]. Eudragit L100 microparticles and pellets have garnered interest to delay drug release and be delivered to a specified site of action [23]. Nadal *et al*. study prepared Eudragit L100 microparticles with ferulic acid with almost spherical shapes (2–3 µm) and smooth surfaces. The particles had a good encapsulation efficiency of nearly 100%. The *in vitro* drug release showed that ferulic acid-loaded microparticles were able to delay drug release at $pH < 6$ and complete dissolution at a pH of 7 [25]. Owing to its unique properties, Eudragit L100 was used in this study to produce pellets of the required physical/ mechanical properties. As there are few studies on pellet characteristics produced from Eudragit L100 matrix and hardly any studies looked at the use of Eudragit based pellets in ODTs while the mechanical properties of the pellets are maintained under compression. Therefore, this study was designed to look at the effect of different particle sizes of Eudragit L100 to achieve smooth and optimized size pellets with delayed IND delivery using orally disintegrating tablets (ODTs) with no IND release in the acidic gastric environment.

## Experimental

### Materials

The materials that were used to prepare the pellets, ODTs and to study IND release studies were as follows: In the pellets preparation: The model drug was IND (Tokyo Chemical Industry, Japan), the polymer was Eudragit L100 (Evonik, Germany), plasticizer was sorbitol (Sigma-Aldrich, France), and deionized water was used as a granulation fluid.

Rhodamine B (Research Chemicals Ltd., UK) as a colouring agent. In ODTs preparation: Low-substituted Hydroxypropyl Cellulose powder (LHPC) (Shin-Etsu Chemical Co., Ltd., Japan) was used as a binder during powder mixing and disintegrant to prepare ODTs, Stearic acid Magnesium Salt (Sigma-Aldrich, Germany) as a lubricant for tablets compression; Lactose monohydrate (Sigma-Aldrich, Netherlands) as a cushioning agent. The following materials were used for HPLC and *in-vitro* release studies: Acetic acid glacial (VWR International, France). Acetonitrile (HPLC – SUPER GRADIENT, VWR chemicals, France). Methanol (VWR chemicals, France). Disodium hydrogen phosphate (Alfa Aesar, Great Britain). Sodium hydroxide and sodium chloride (Fischer Scientific, UK). Potassium phosphate monobasic (Honeywell Fluka, Spain).

## Sieve Analysis

An accurately measured amount of Eudragit L100 (100 g) was sieved using a vibratory sieve shaker (Retsch, Germany) with mesh sizes from 1000 µm to 45 µm. The sieve shaker vibrated at 1.5 mm amplitude for 10 min. The particles on each sieve were collected and weighed. The particle sizes of 90 µm, 63 µm and 45 µm were separated for further use in this project.

## Powder Flowability

The flowability of Eudragit L100 with all particle sizes was measured to assess the ability of the particles to settle and compress. Compressibility index, Hausner's ratio and tapped density were used to assess the flowability and the ability of the particles to settle during pellets preparation and select the powder of good values to prepare the pellets. The compressibility index and Hausner's ratio were calculated for the collected particles using a graduated measuring cylinder and around 10 g of powder. Also, tapped density was measured using Erweka tapped density tester (ERWEKA GmbH, Germany) applying 10, 500 and 1250 strokes according to the United States Pharmacopeia (USP) method and volume readings were recorded until no to little further volume change was noticed. Compressibility index and Hausner ratio were calculated according to Eq. 1 and Eq. 2, respectively.

$$\text{Compressibility index } (\%) = \frac{\text{Apparent volume} - \text{Tapped volume}}{\text{Apparent volume}} \times 100 \quad (1)$$

$$\text{Hausner ratio} = \frac{\text{Apparent volume}}{\text{Tapped volume}} \quad (2)$$

## Pellet Preparation

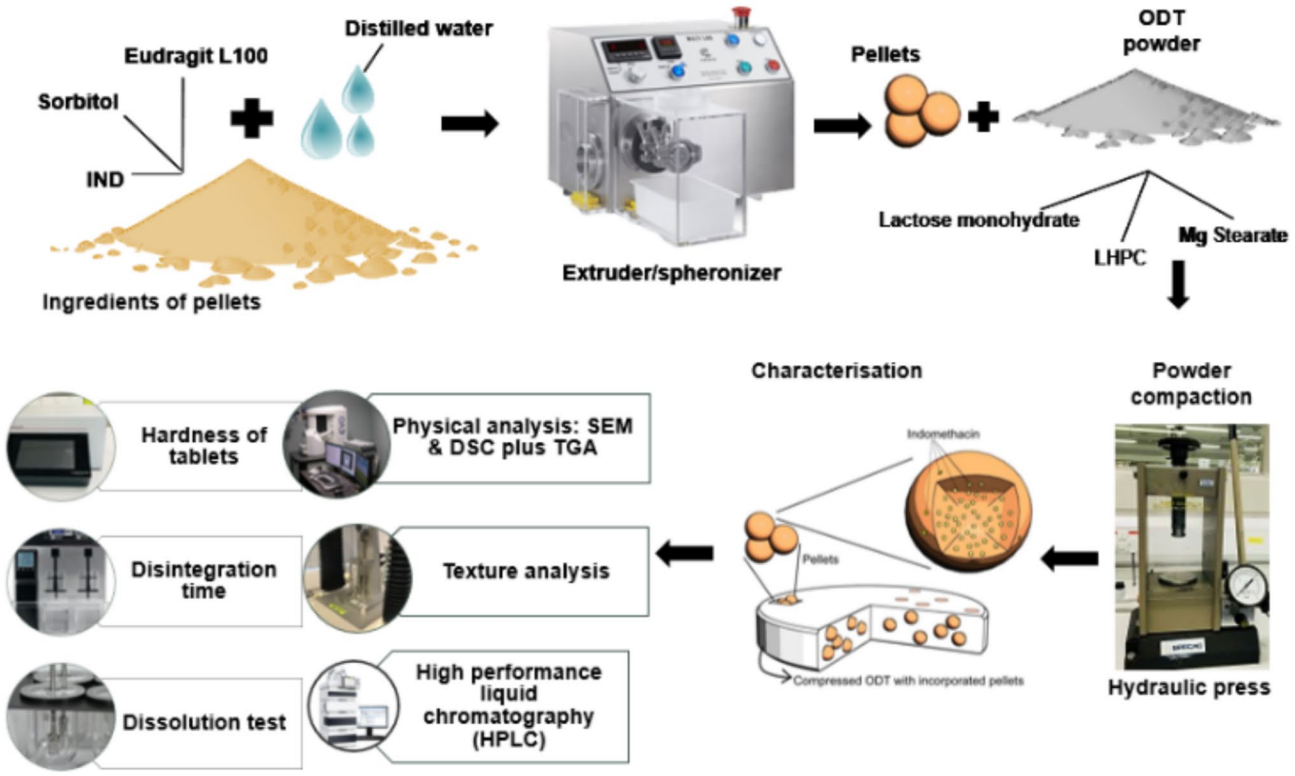
The extrusion spheronization process was used as a lab-scale instrument (Caleva process solutions Ltd, UK). Preliminary studies to investigate the physical properties of the IND in combination with excipients were performed using Eudragit L100 raw powder without sieving. The ingredients amount in w/w was 5% of IND, 30% of sorbitol, and 65% of Eudragit L100 with water as a granulation fluid (1.9 mL). The control batch was prepared from raw Eudragit L100 using similar matrix constituents to compare with other batches and indicate the optimum properties. The sieved Eudragit L100 powder of each particle size 45, 63 and 90 µm was used in pellets preparation with the previously mentioned quantities producing the other three batches. All the dry excipients for each batch were put into the mixer (Caleva Multi Lab, Process Solutions Ltd, UK), and then Eudragit L100 powder was mixed for 10 min at a speed of 180 rpm before the addition of water. After the addition of water, the wet mass was mixed for 10 min simultaneously until the wet mass's texture became like breadcrumbs.

The wet mass was transferred to the extrusion platform that holds a single screw extruder set at 60 rpm. The wet mass was slowly poured into the extrude and pushed towards the extruder screen. The screen has holes of 1.0 mm × 1.0 mm in diameter and 26 holes in total. Cylinder-shaped extrudates were formed and collected. After that, extrudates were poured into the spheronizer to prepare pellets with spherical shapes at speed of 1200 rpm for 10 min. The final stage of pellet preparation was drying. The pellets were collected in a glass petri dish, distributed as a monolayer, and then placed in the oven (Copley Termaks, Norway) at 40–50°C for 2 h. After drying, the products were put in sealed vials and kept in a desiccator to prevent any possible interactions with the atmospheric moisture until further characterization as highlighted in Scheme 1.

## Physical Characterization

### Size and Sphericity

Pellet sphericity, shape and size were determined using a caliper (Carbon Fiber Composite Digital Caliper, China, 0.1 mm-100 mm). The diameters of 25–30 of the produced Eudragit L 100 containing pellets were measured with the




**Scheme 1** Summarises the key pellets and tablets preparation and characterisation process

caliper, and the aspect ratio (AR) was calculated according to Eq. 3, where "L" is the longest diameter, and "S" is the shortest diameter [26, 27].

$$AR = \frac{L}{S} \tag{3}$$

### Percentage Yield, Flowability, Bulk Density and Porosity

The yield is the produced amount of the pellets that were calculated using Eq. 4, which was based on the weight of the prepared pellets (Pellets Pw) divided by the weight of the solid materials used in the preparation of the pellets (Sw).

$$\text{Yield } (\%) = \frac{P_w}{S_w} \times 100 \tag{4}$$

The bulk density was measured for Eudragit L100 powder (45, 63 and 90 µm) and the obtained pellets were prepared from each particle size using Eq. 5 with 5 g material poured into a 10 mL graduated cylinder and the volume was measured. Further, flowability was evaluated for the produced pellets using Erweka GTL Powder and granulate flow tester (Erweka, Germany). A total of 10 g of pellets were accurately weighed and placed into the Erweka GTL flow tester and the results were recorded in the amount of poured sample in "g" per second.

$$\text{Bulk density} = \frac{\text{Weight of sample}}{\text{Bulk volume of the sample}} \tag{5}$$

Porosimeter, Belsorp II (Belsorp mini, BEL Japan Inc., Japan) was used to evaluate the porosity of Eudragit L100 powders and the produced pellets. An accurately weighed sample was placed into the sample's cells, which were then pre-treated for 2 h at 40°C to remove moisture. The cells were purged using helium gas, samples were weighed following pre-treatment, and the weight of the sample was recorded. Then the treated samples were exposed to liquid nitrogen (77K) and the related isotherms were collected using Belsrop software and Brunauer–Emmett–Teller equation to illustrate the relationship between the adsorption volume and the relative pressure from nitrogen adsorption [28].

### Morphology and Shape

Evaluating the shape of the prepared pellets is an essential factor that affects the pellets' physical properties, which was completed using stereomicroscopy and scanning electron microscopy (SEM). The microscope (Nikon Corporation,

Japan) was used to assess the pellets' shapes and sizes as well as the final ODTs. The images were analyzed via the installed software (NIS-Elements Viewer, Nikon Corporation, Japan). Furthermore, SEM images for Eudragit L100 powders, the pellets and produced ODTs were captured using Zeiss Evo50- SEM (Oxford instrument, UK). A few milligrams or few pellets were sprinkled on a double adhesive carbon sheet placed on a clean stub then coated with gold at a low vacuum for 3 min using the sputtering coater was carried out under argon gas (Polaron Equipment, Watford, UK). SmartSEM software (Zeiss Evo50- Oxford instrument, UK) was used to analyse the images.

## Pellet Mechanical Properties

Determination of the elasticity of powders and pellets was evaluated using the texture analyzer (Stable Micro Systems, UK) and exponent software. A small sample was placed into the die and the rig-probe was used for powder compaction. The strain height was set at 20 mm, the stress area at 28.3 $mm^2$, the die diameter at 6 mm, the upper punch speed at 1.00 mm/s and a compression force of up to 300 kg. The results were recorded as a function of applied stress (MPa) as per unit area *versus* deformation (strain (%)). Young's modulus (YM) was calculated based on Eq. 6 [29].

$$\text{Young}'\text{s modulus} = \frac{\Delta \text{ Stress}}{\Delta \text{ strain}} \tag{6}$$

The other property measured for all pellets batches is hardness using the texture analyzer (Stable Micro Systems, UK) and exponent software. An individual pellet was examined by placing it on a flat stainless-steel base which was subjected to 5 kg force at a rate of 0.5 mm/s using the stainless-steel cylindrical probe (35 mm diameter). Equation 7 was employed for the calculation of the tensile strength of the pellets (25–30 pellets/batch), where "F" (N) is the crushing force, "r" (mm) is the radius of the pellets [30–34].

$$\text{Tensile Strength} = \frac{0.4F}{\pi r^2} \tag{7}$$

## Thermal Analysis

Differential Scanning Calorimetric analysis (DSC) for the produced pellets, Eudragit and IND was carried out using DSC Mettler Toledo, DSC822e (Switzerland). Accurately weighed 4–5 mg samples were placed in an aluminum crucible and covered with a lid. Samples were evaluated under nitrogen gas and temperatures ranging from 30 to 300°C at a heating rate of 10°C/ min. The data were analyzed using STARe software (Mettler Toledo, Switzerland). The thermogravimetric analysis (TGA) was carried out using Mettler Toledo SDTA/TGA 851e, (Switzerland) and both moisture content and degradation temperatures of all samples were evaluated at heat flow of 10°C/minute and temperature ranging from 20°C to 400°C under nitrogen gas. 5 mg of each sample was placed in an open alumina crucible. Thermograms were collected using STARe software (Mettler Toledo, Switzerland).

## Preparation of ODTs

A matrix of ODTs was prepared using 74% Lactose monohydrate as a filler, LHPC as a disintegrant in 25% and 1% magnesium stearate as a lubricant during tablet compression. All pellet' batches were mixed with ODT matrix, including 10% (50 mg) pellets and 90% ODT matrix. A Turbula mixer (Willy A. Bachofen AG, Muttenz, Switzerland) was used to mix the ODTs matrices and the delayed-release pellets at 50 rpm for 10 min. Similarly, the control tablets were prepared using IND powder with no pellets. Then, the delayed-release pellets-ODTs (DRP-ODTs) mixture in 500 mg each and control ODTs were compressed using a manually controlled uniaxial hydraulic press (Specac tablet presser, Slough, UK) with 13 mm die at 1-ton force over 10 s as dwell period.

## High-Performance Liquid Chromatography (HPLC) Analysis

The quantification of IND was carried out using a validated HPLC method. Agilent Technologies ll HPLC, (USA) and Lab Software (Agilent OpenLab CDS, Agilent, USA) were employed for the analysis. The method was carried out using HPLC column 00F-*4420-E0* HyperClone™ 5µm, BDS C18 130A° of dimensions 150 × 4.6 mm (Phenomenex, USA). The flow rate was set at 1 mL/min with 20 µL of sample volume. The mobile phase was made up of (30:70) (v/v) of 0.1 M acetic acid and acetonitrile, and peaks were captured at 248 nm. The validation of IND was conducted according to the ICH guideline, Q2 (R1) [35], in terms of accuracy, precision (inter and intraday precision), specificity, linearity, range, limit of detection (LOD), and limit of quantification (LOQ). IND was eluted at 2.3 – 2.4 min.

## Characterization of the ODTs

The mechanical properties of the produced DRP-ODTs and control ODTs were evaluated by testing tablets' hardness. The tablet's thickness and diameter were measured using a digital caliper. All tablets ($n = 3$) were placed individually on a tablet hardness tester (Pharmatron AG, Switzerland), and results of crushing force were recorded for each tableted formulation. The values are the applied force (N) to break a tablet. The hardness of tablets and the tablet dimensions

were recorded to calculate tensile strength as in Eq. 8, where F is the force, D and T are the diameter and thickness of the tablet.

$$\text{ODTs Tensile strength} = \frac{2F}{\pi\, D\, T} \quad (8)$$

Further, disintegration time was evaluated using a disintegration tester (Erweka ZT3, Germany) for triplicate for each batch in 500 mL of deionized water set at 37 ± 0.5°C. The *in-vitro* release studies for the pellets and ODTs were carried out in two dissolution media: acidic media (pH 1.2) and buffer media (pH 6.8) using USP type II paddle dissolution apparatus holding 900 mL of the designated media and temperature was kept at 37.0 ± 0.5°C. Samples (5 mL) were collected at various intervals and then replaced with the same volume from the *in vitro* release media. The samples were filtered using a 45 µm micropore filter into HPLC vials before the analysis. All the samples were analyzed using the established HPLC method ($n = 3$).

### Statistical Methods

Results were analyzed using Microsoft Excel software. Analysis of variance (one way ANOVA) and a paired t-test to show the difference between the batches at significance level 0.05 ($P < 0.05$) using Minitab software version 21.10.1. A minimum of 3 samples were run and the results of the statistical analysis for all formulations were presented as Mean ± standard deviation (SD).

## Results and Discussion

### Powder Characterization

Successful solid oral dosage forms depend on the primary materials' properties to prepare the final formulation. To prepare a well-compacted system of delayed-release IND pellets to be used in the ODTs, we prepared the IND pellets from different Eudragit L100 particle sizes (45, 63 and 90 µm) and examined the effect of the particle sizes of the pH-dependent polymer and their physical/ mechanical properties. Various characterization techniques were employed. The selection of the particle size was based on preliminary particle size analysis where 45, 63 and 90 µm were the most abundant particles with percentages of 18.7%, 46.49% and 26.76% respectively.

#### Powder Flowability And Density

In pellet preparation, adhesive and cohesive forces can be generated between the Eudragit L100 particles as well as between Eudragit L100 and other excipients respectively, which can cause particle agglomeration [36]. These forces can include solid bridges, electrostatic force, and liquid bridges from the moisture content [37]. The contribution of the attraction forces can vary depending on different factors such as particle size, shape, bulk density, surface area, and mechanical properties, which affect the quality of the pellets. Furthermore, irregular surfaces lead to interlocking bonding and forming agglomerates [36]. Hence, particles with rough or fissured surfaces agglomerate through interlocking bonds [20]. Therefore, evaluating powder particles' physical properties is essential.

Flowability was measured to assess the ability of the particles to settle and compress. The compressibility index and Hausner's ratio of all Eudragit L100 particle sizes were studied, and the results are summarized in Table I. The flowability results showed that the flow properties of all particles were acceptable, ranging between excellent and fair, to be selected in pellet preparation. Although powder of 45 µm showed fair flowability, the bulk and tapped density were close to other sizes' values and no significant difference was observed (SD was zero). Moreover, only for the materials of poor flowability, a remarkable difference between bulk and tapped densities can be noticed as such, these materials are not preferable to be used in forming compacts [38]. Loh, Samanta and Sia Heng reported a similar trend, where particles lower than 30 µm tend to have more cohesive forces and reduced powder flow [36].

#### Morphology and Size of Powder Particles

Stereomicroscope and SEM analysis were used to detect all polymer particles' sizes and morphological characteristics. The microscope images showed the difference in Eudragit L100 particle sizes which was correlated with the sieve analysis confirming the accuracy of the method to collect

**Table I** Compressibility Index and Flow Properties of Eudragit L100 45, 63, 90 µm Powders

| Sample name | Compressibility index (%) | Hausner's ratio | Bulk density gm/mL ($n = 3$) | Tapped density gm/mL | Flow character |
|---|---|---|---|---|---|
| Eudragit L100 45 µm powder | 16 | 1.19 | 0.50 | 0.59 | Fair |
| Eudragit L100 63 µm powder | 12 | 1.13 | 0.50 | 0.57 | Good |
| Eudragit L100 90 µm powder | 8 | 1.08 | 0.50 | 0.54 | Excellent |

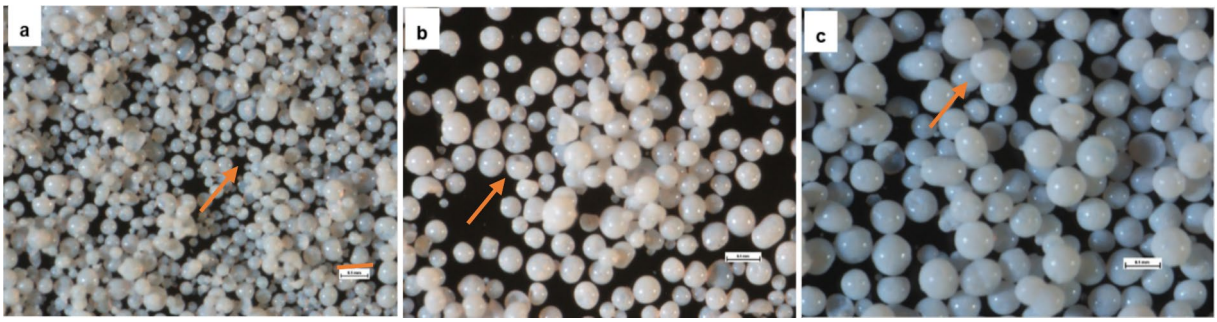



**Fig. 1** Eudragit L100 powder with particle sizes of 45 µm (**a**), 63 µm (**b**), and 90 µm (**c**) using a stereomicroscope. The scale is 0.1 mm. Arrows are annotating some of the Eudragit L100 particles demonstrating the differences in size and shapes

the powders of variant sizes. Also, most of the particles had spherical shapes and smooth surfaces (Fig. 1), which was an effective factor in producing a wet mass of good consistency as the first stage of pellets development.

The other method employed to distinguish between the particle sizes and morphology was SEM (Fig. 2). It can be seen from SEM images the differences in particle sizes of the powder particles and the presence of some other small

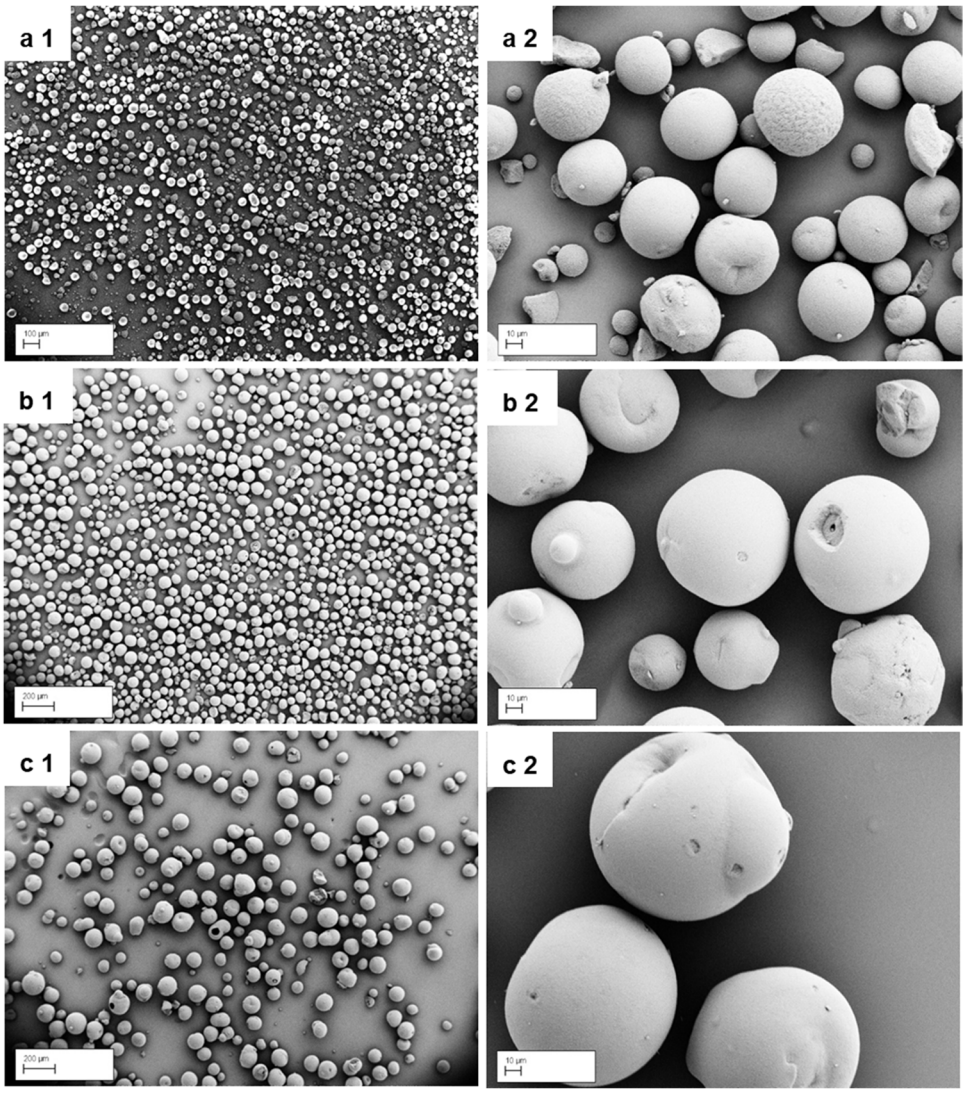



**Fig. 2** SEM images at low and high magnification showing the Eudragit L100 powder particles with particle size of 45 µm (**a1**, **a2**), 63 µm (**b1**, **b2**) and 90 µm (**c1**, **c2**)

particle sizes, which can be related to the fact that the small particles can agglomerate and interlock during the sieving process. Shi, Hao, *et al.* found that particle cohesiveness decreases with increasing particle sizes which was noticed with Eudragit L100 powder particles in our study [39]. Also, the other factor that can be considered for optimizing the sieving method is to increase the sieving time [40]. However, the analysis was performed according to ICH guidelines, and the findings did not markedly affect the powder particle size properties due to the explicit differences between the compressibility and flowability of the powder.

### Texture Analysis

The elasticity profile of Eudragit L100 particles was carried out (Table II). The ability of the material to form a compact depends on its tendency to deform permanently (plasticity) or temporarily (elasticity). YM, which is the relationship between the applied stress on the martial particles and the strain (change in dimensions), was used to measure the elasticity of particles and their ability to protect their shapes under the applied force. The texture analyser with a maximum force of 300 kg was used, and the obtained graph was extrapolated to calculate the gradient (stress/ strain). All particle size batches showed low YM values contributing to good elastic properties as lower YM's values resulted in higher elasticity [41]. Although the values were different, YM values were low, and there was no significant difference (one-way ANOVA, $p = 0.38$, *and Tukey post-hoc test* $p > 0.05$). Therefore, YM values reflected the good properties of Eudragit L100 particles to resist compression regardless of the particle size. Thus, they were used in pellets' preparation.

### Porosity

The original excipient properties can affect the prepared pellets' physical and mechanical properties. Therefore, the porosity of the Eudragit L100 was measured for all particle sizes (Table III). The 63 µm particles had almost similar porosity results to that of the non-sieved Eudragit L100 powder. This similarity was correlated with sieving data as the particles of 63 µm had the highest collected weight (retained) and high cumulative oversize, among other particles. Moreover, the porosity results are considered acceptable and showed a low effect on the powder's mechanical properties. According to YM results, all particle sizes showed low YM with no significant difference ($p > 0.5$). Similarly, all batches (45, 63, 90 µm) had low bulk densities with similar values ($p > 0.5$), which were not affected by Eudragit L00 powder porosity. Nevertheless, the slight difference in porosity can be related to the difference in particle sizes, which can be seen in SEM images. Hence, the smaller the particle size, the more compacted surfaces could be noticed later in the pellet section [42]. Finally, the particles had a pore diameter between 2- 50 nm demonstrating mesoporosity. Hence, surface area and total pore volume are proportional [43].

**Table II** Texture Analysis Results for Eudragit L100 Powder 45, 63 and 90 µm ($n = 3$) Showing the YM as Elasticity Profile Analysed with Exponent Software

| Sample name | YM (MPa) (mean ± SD), $n = 3$ |
|---|---|
| Eudragit L100 45 µm powder | 4.376 ± 0.619 |
| Eudragit L100 63 µm powder | 4.751 ± 0.502 |
| Eudragit L100 90 µm powder | 4.97 ± 0.277 |

**Table III** Porosity Measurements for Eudragit L100 Raw Powder, 63 µm and 90 µm Particles using Belsorp Analysis and BET Equation

| Sample | surface area ($m^2 g^{-1}$) | Total pore volume ($cm^3 g^{-1}$) | mean pore diameter (nm) |
|---|---|---|---|
| Eudragit L100 powder | 2.280 | 0.051 | 8.97 |
| Eudragit L100 63 µm powder | 2.285 | 0.062 | 10.94 |
| Eudragit L100 90 µm powder | 2.249 | 0.059 | 10.53 |

## Pellet Characterization and Micrometric Properties

Three batches of Eudragit L100-based pellets were prepared with different particle sizes (45 µm, 63 µm and 90 µm) using sorbitol as a plasticizer and water as granulating fluid. Extrusion spheronization was used to prepare all the batches. The pellets were evaluated according to yield, flowability, shape, size, porosity, and mechanical properties.

Initial studies investigated the best amount of water and plasticizer needed to produce good pellet yield with an aspect ratio close to 1 using the non-sieved Eudragit L100 powder. The results as depicted in Table IV showed that the process was highly reproducible and with low standard deviations using the lowest amount of water to obtain pellets

**Table IV** Pellets of Eudragit L100, Sorbitol and IND, A, B, and C batches have 5%, 15%, and 30% (w/w) of Sorbitol Showing Water Amount, AR (Aspect Ratio) ($n = 10$) and Yield (* Significant Difference)

| Sample | Water (mL) | Mean AR ± SD | Total Yield (%) |
|---|---|---|---|
| Batch A | 4.1 | 1.36 ± 0.377* | 26.32 |
| Batch B | 2.6 | 1.98 ± 0.423* | 70.99 |
| Batch C | 1.9 | 1.26 ± 0.232* | 45.50 |

of 30% sorbitol. The AR demonstrated significant difference among batch (one-way ANOVA, $p=0.0002$), using Tukey ad hoc analysis, the results showed that the difference is significant between batch A and B ($p=0.0015$) and batch A and C ($p=0.003$), while insignificant between batch A and B ($p=0.803$).

### The Effect of Particle Size on the Yield, Bulk Density and Flowability

The produced pellets using various Eudragit L100 powder with particle sizes (45, 63, 90 µm) showed good yield (Table V). The pellets made from 45 µm Eudragit L100 had the lowest yield, 58%, while the highest was 66%, for the 90 µm batch among the prepared pellets from sieved powders. This difference can be related to the difference in particle sizes of the initial powder as the small-sized particles tend to aggregate, forming agglomerates of strong adhesion forces that were difficult to extrude, which was noticed in our study [44]. Also, when particle size was reduced, the surface area increased and the generated interparticulate forces between the fine particles increased [45]. Moreover, the AR of the pellets was lower than 2 and all the batches showed acceptable sphericity (Table V). However, the pellets with high sphericity were obtained from the 90 µm batch (AR 1.25) which was close to the reference value of the non-sieved powder pellets (AR 1.30). The AR values were significantly different between batches ($p<0.5$) (45, 63 & 90 µm). Although 45 µm and 63 µm batches showed higher AR (1.52 and 1.49), the difference was insignificant ($p=0.76$).

The flow property can significantly affect pellets' quality in tablet preparation [46]. Besides, the material's packing ability is measured by its bulk density, and any difference in bulk density can influence packing volume [47]. In general, all batches showed low bulk density, between 0.53–0.66 g/mL, and a flow rate of 4.5 to 5.1 g/sec, as depicted in Table V. Low bulk density could be related to large voids between the packed particles of larger size [48]. It was reported that pellets with low bulk density < 1.25 g/cm$^3$ had good flowability [46, 49]. Therefore, in our study, the pellets showed good flow properties. Furthermore, the good flowability is also attributed to the pellets' good sphericity since AR for all pellets is lower than 2. The difference between the batches can be attributed to the improved sphericity of pellets 90 µm compared to other sizes.

Moisture content difference between the batches could be correlated to particles sizes variance and their ability to retain water. This ability depends mainly on the porosity and surface area of the particles. Therefore, it can be noticed that pellets 63 µm batch had higher moisture content (6.05%) compared to other batches, which is correlated with the high surface area of the original particles (2.285 m$^2$ g$^{-1}$). Overall, the value of moisture content is acceptable for all batches.

### Morphology, Size, and Porosity

The pellets top overview and their AR were recorded for Eudragit L100 45, 63 and 90 batches, as shown in Fig. 3. SEM images showed that the pellets morphology and AR are in harmony with that of the manual method (caliper). Further, the images showed a difference in surface roughness between sizes. The pellets from the 90 µm batch showed a porous and rough surface when compared with the other sizes. The results agreed with pellet porosity results as the 90 µm batch showed the highest specific surface area and pore volume 5.26 m$^2$ g$^{-1}$ and 0.01 cm$^3$ g$^{-1}$ respectively (Table VI). The pellets were explicitly detected after compression within tablets, as in Fig. 3(d), showing a pellet of the 90 µm batch embedded in the ODTs.

In comparison, the 45 µm batch had a smooth and less porous surface, which is correlated with porosity and surface area results (3.26 m$^2$ g$^{-1}$) and pore volume (0.007 cm$^3$ g$^{-1}$). The porosity of 63 µm pellets was intermediate among pellets, while the initial powder of 63 µm had high porosity and specific surface area. Moreover, other factors can affect the porosity, such as AR, moisture content and extrusion spheronization parameters (e.g., time and speed). The lowest AR (1.25) correlated to a small diameter (1.21 ± 0.27 mm) demonstrated by a 90 µm batch, leading to the high surface area. Also, since all materials had a mean pore diameter between 2–50 nm, these formulations are mesoporous. Therefore, the mesoporous martial tends to show monolayer and multilayer as part of the Type IV isotherm.

**Table V** Physical and Micrometric Properties of Eudragit L100 Pellets Prepared used Different Particle Sizes of 45, 63 and 90 µm

| Batch | Aspect ratio (Mean ± SD) ($n=30$) | Yield % | Moisture content % | Bulk density gm/mL ($n=3$) | Flow rate (g/sec) ($n=3$) |
|---|---|---|---|---|---|
| EudargitL100 pellets | 1.30 ± 0.25 | 72% | 6.58% | 0.66 ± 0.04 | 4.5 ± 0.50 |
| EudargitL100 45 µm pellets | 1.52 ± 0.37 | 58% | 4.09% | 0.53 ± 0.01 | 4.3 ± 0.02 |
| EudargitL100 63 µm pellets | 1.49 ± 0.26 | 61% | 6.05% | 0.53 ± 0.02 | 4.3 ± 0.10 |
| EudargitL100 90 µm pellets | 1.25 ± 0.17 | 66% | 5.11% | 0.56 ± 0.04 | 4.93 ± 0.40 |

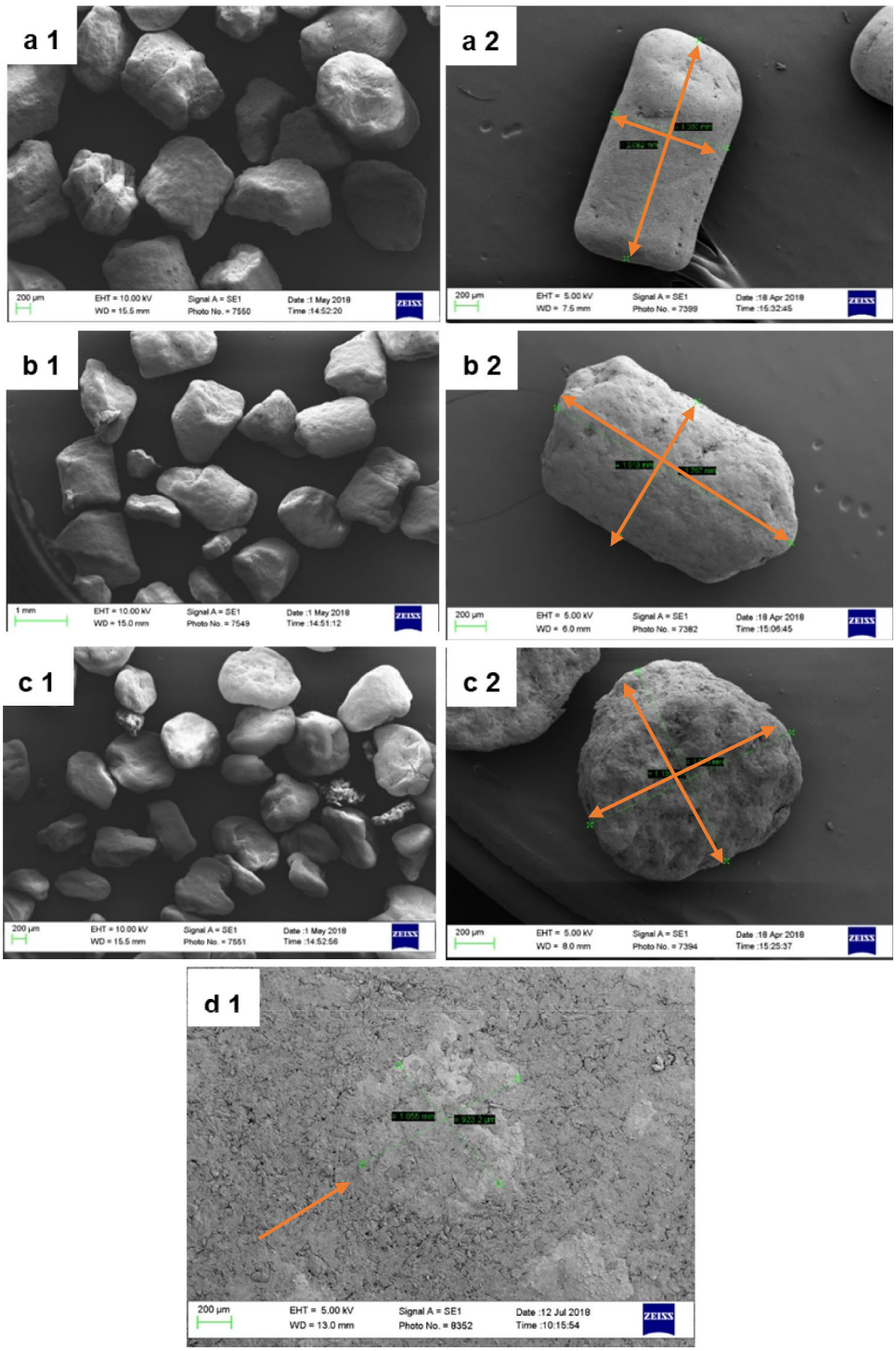



**Fig. 3** Pellets of Eudragit L100 showing (**a1**) general overview of pellets made from 45 µm Eudragit L100 (**a2**) 45 µm batch AR, (**b1**) general overview of pellets made from 63 µm Eudragit L100 (**b2**) 63 µm batch AR, (**c1**) general overview of pellets made from 90 µm Eudragit L100 (**c2**) 90 µm batch AR (**d**) Top overview for pellets of 90 µm batch embedded in ODT showing AR using SEM. Arrows are annotating some of the pellets within the ODTs matrix or to show the aspect ratio of the pellets

## Mechanical Properties of Pellets

The mechanical properties represented by YM, and tensile strength were measured using the texture analysis method for pellets. The temporary deformation and fragmentation of pellets during compression are relatively correlated with the starting materials' fundamental mechanical properties such as elasticity and plasticity [50]. It is necessary to consider the elastic–plastic properties of the material and determine the optimum batch. High tensile strength values could indicate brittle materials that suffer fragmentation, while a high degree of plasticity provides irreversible compacts with deformed shapes [51]. Particles with elastic properties, irreversibly return to their shape after compression [52]. Therefore, a balance between elastic and plastic properties can improve the pellets' compaction by retaining their shape

**Table VI** Porosity and Surface Area Data for All batches of Pellets Prepared from Raw Eudragit L100 Particles (45,63 and 90 µm)

| Sample | surface area ($m^2\ g^{-1}$) | Total pore volume ($cm^3\ g^{-1}$) | Mean pore diameter (nm) |
|---|---|---|---|
| Pellets Eudragit L100 | 4.51 | 0.007 | 7.04 |
| 45 pellets Eudragit L100 | 3.26 | 0.007 | 8.24 |
| 63 pellets Eudragit L100 | 4.44 | 0.009 | 7.82 |
| 90 pellets Eudragit L100 | 5.26 | 0.01 | 7.67 |

after compression with no fragmentation. Therefore, maintain the functionality of prolonged release ODTs. This allow the ODTs matrix to disintegrate in the buccal cavity facilitating ease of swallowing, while the incorporated pellets will maintain their integrity stopping the release of IND in the upper GIT and blocking the harmful side effects of the drug.

In addition, the physical properties of the primary particles such as porosity, shape and density can affect the compression of the formed or compressed pellets [53]. Also, tensile strength increases with increasing packing density of particles due to the increase in the number and intensity of interparticle forces (adhesion, cohesion, interfacial, bridging and interlocking) [54]. Similarly, this was noticed in our results as the highest bulk densities were obtained from Eudragit L100 and 90 µm pellets 0.66 and 0.56 gm/mL, respectively. Although the 90 µm batch showed high porosity compared to the other batches, the porosity was still relatively low, showing a limited difference and no effect on IND release as in the following sections. However, other factors could be considered, such as the pellets' dimensions as the shortest diameter pellets could offer large surface area and provide high interparticulate binding sites resulting in strong bonds resisting the applied pressure [55]. Therefore, the 90 µm based pellets showed the highest tensile strength among the pellets of sieved powders. Also, the low AR and the small diameter of 90 µm batch rendered the pellets' high surface area, leading to increased hardness and eventually tensile strength. A similar trend was noticed with the YM value, which is the relationship between the applied stress and strain, as the AR of the pellets indirectly affected YM [50].

This finding could explain the significant difference between 45, 63 & 90 µm batches ($p = 2.78E\text{-}12$) in the hardness values while pellets 45 µm and 63 µm showed no statistical difference ($p = 0.666$) (Fig. 4). In addition, the high surface roughness associated with the 90 µm batch could lead to an interlocking mechanism offering high strength with the tablet's matrix or other pellets [54]. This was detected in the tablet's mechanical strength section. However, the difference showed limited effect with low compression pressure. Looking at the porosity and the surface area of pellets with different sizes (Table IV), it is noticed that increasing the pellet size was associated with an increase in the pore volume and surface area. A similar trend was observed when looking at the mechanical properties of these pellets. As the tensile strength increased from $3.89 \pm 0.68$ to $4.16 \pm 0.61$ and $5.15 \pm 0.72$ for the 45, 63 and 90 µm respectively (Fig. 4).

## Thermal Analysis

The produced pellets of Eudragit L100 (45 µm, 63 µm and 90 µm) were characterized to examine their thermal behavior using DSC and TGA analysis techniques. The DSC thermograms showed that the physical mixture of the formulations had no chemical interaction with IND (Fig. 5(a)). Hence, the melting point of IND at 162°C was detected in all tested pellets [56]. Although the peak area of the pellets batches

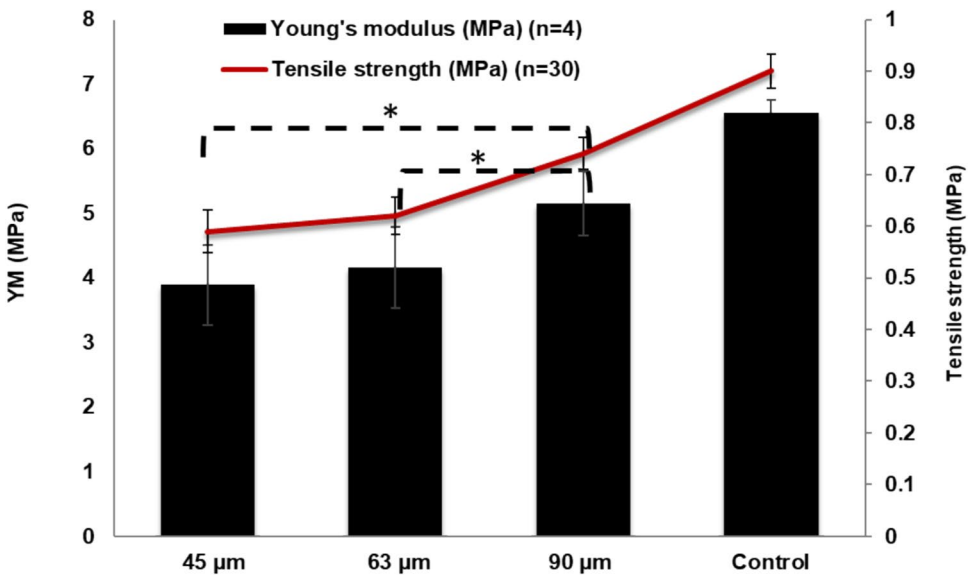



**Fig. 4** Graph of mechanical properties of pellets prepared from 45, 63, 90 µm and raw powder of Eudragit L100 (control) showing YM and tensile strength in mean ± SD

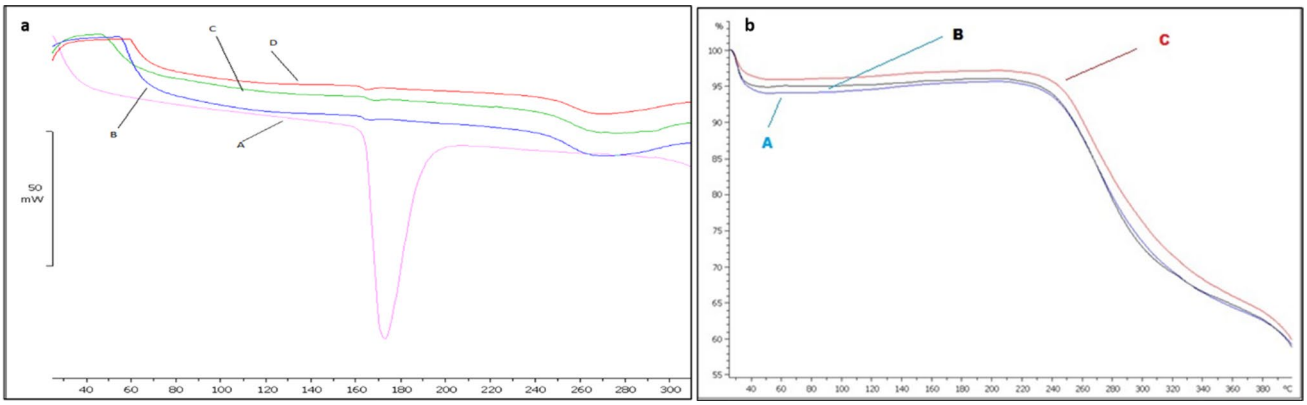



**Fig. 5** (**a**) DSC graph of indomethacin (**A**), pellets of 90 µm (**B**), 63 µm (**C**), 45 µm (**D**) EudragitL100 powder using Mettler Toledo and STARe software, (**b**) TGA Thermogram of EurdagitL100 pellets of 63 (**A**) & 90 (**B**) 45 (**C**) µm showing the moisture content orderly and the degradation temperature

was different from that of the pure drug, the quantity of the IND used was low (5%) and the predominant effect of polymer (65%) correlated with the preparation method of pellets. Moreover, the slight deviation in the melting point of the formulation could be attributed to the plasticization effect of sorbitol. Atef *et al.* noted in DSC results that the melting point for the gamma form of IND was between 160–162°C while alpha form had a melting point of 152–154°C [57]. Therefore, IND in our formulation could be the gamma form.

Moreover, Eudragit L100 amorphous state was confirmed by the absence of the endothermic peak of melting point [58]. The peak around 230–240°C could be related to the degradation [59]. It was reported that Eudragit L100 $T_g$ was around 200°C [59, 60]. However, the value may vary depending on storage conditions and the manufacturer. All pellets demonstrated degradation after 220°C as in the TGA thermogram (Fig. 5(b)). Therefore, the endothermic peak in the DSC graph is related to the starting of polymeric degradation [60, 61].

Moisture content was measured using TGA thermograms, and the results of all batches showed a difference in moisture content. This can be attributed to the behaviour of the primary materials and the difference in particle sizes. The high porosity of both raw powders of Eudragit L100 and that of 63 µm is associated with the ability of the particles to retain water, demonstrating high moisture content for the produced pellets 6.58 & 6.05% consecutively (Fig. 5(b)). ALL pellets had good moisture content (less than 7%), yet the excellent balance of 90 µm batch mechanical properties correlates with low moisture content. Although the 45 µm batch showed the lowest moisture content, the pellets showed the lowest mechanical properties.

This can be related to two explanations: firstly, the low surface area and pore volume of pellets (according to porosity results) show minimum filled voids (with gas or water) between the particles, which was confirmed from the smooth surfaces in SEM. Secondly, the moisture content can behave differently among the particles. Thus, the moisture content is necessary to be within a specific range to produce pellets with the desired properties [62]. Briefly, moisture content can exist in three phases tightly bonded to the particles, weakly bonded or as bulk water. When moisture increases, the tensile strength of compact increases due to solid bridges between the particles or particle–particle interaction. However, when the water molecules exist at particle surfaces, acting as a lubricant can reduce the attraction of the particles, thereby tensile strength. Therefore, low moisture content can reduce the tensile strength as seen in the 45 µm batch [62].

## DRP-ODTs' Characterization

The obtained pellets from all Eudragit L100 sizes (45 µm, 63 µm and 90 µm) were used to prepare ODTs. The tablets included 10% (w/w) of pellets. The prepared tablets were evaluated to assess the morphology, hardness, disintegration, and IND release profile.

### SEM Analysis and Stereomicroscope

The ODTs were analyzed using SEM to investigate the tablet matrix before and after compression (Fig. 6). The stereomicroscope was used to identify the pellets within the tablet's matrix and detect AR pellets (Fig. 7). Also, the cross-section view for all batches was examined using SEM and stereomicroscope to detect the pellets within ODT matrices, as in Fig. 7 and Fig. 8. Rhodamine B was used when preparing the pellets to enable visual identification of the formed pellets after compression.

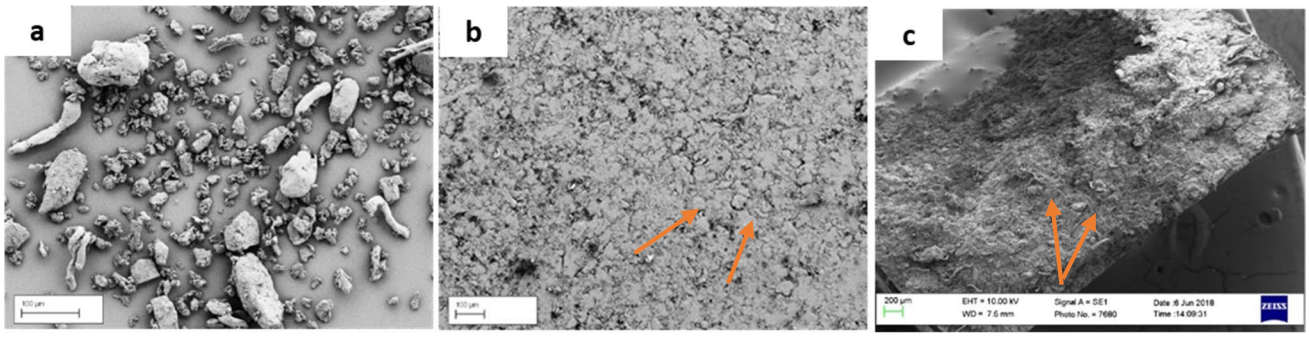



**Fig. 6** SEM images highlighting, (**a**) the powder of ODT before compression, (**b**) the compressed ODT top view and (**c**) cross-section of the ODT. Arrows are annotating some of the pellets within the ODTs matrix/ on the surface

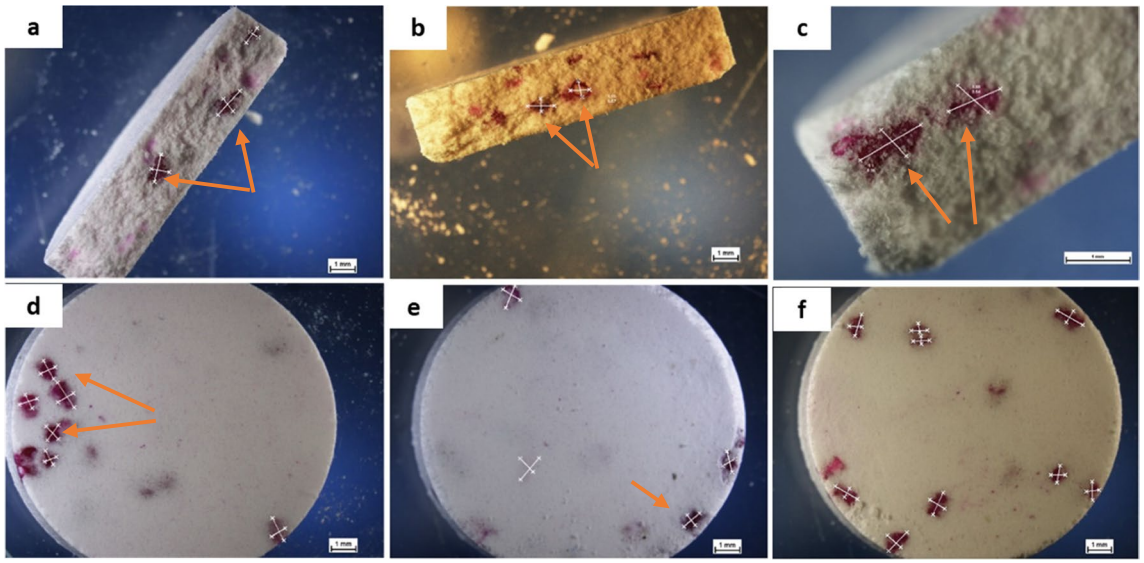



**Fig. 7** Stereomicroscope images of DRP-ODTs showing cross section view and top view of the tablets of 45 µm batch (**a** & **d**) 63 µm (**b** & **e**) 90 µm (**c** & **f**) batches accordingly. Arrows are annotating some of the pellets within the ODTs matrix/on the surface

The results in Fig. 6 showed the shape of the starting material as elongated particles with rough surfaces that can provide good disintegration time. Hence, the ODT matrix consists mainly of LHPC (disintegrant) and Lactose monohydrate (binder and diluent), which can be noticed from the rough surfaces of ODT. During DRP-ODTs preparation, the mixing of ODTs matrices and the pellets was challenging due to the difference in particle sizes of the ODT matrix, the large size of the pellets and the non-uniform shapes of initial particles forming the ODT matrix. Therefore, this was considered through increasing mixing time and evaluating IND release from the uncompacted pellets to be compared with the DRP-ODTs release independently, as in the next section. Moreover, stereomicroscope images (Fig. 7) indicated the presence of the pellets embedded in the matrix distinctly.

AR obtained from the microscope was correlated with the caliper results. All pellets were detected successfully within the ODTs matrix showing retained shape under compression as detected in for ODTs before and after the hardness test (Fig. 7 and Fig. 8).

### The hardness of the Tablets and disintegration time

The DRP-ODTs hardness was detected using the hardness tester, and the results were recorded for extrapolating tensile strength [50, 62]. Also, all batches of DRP-ODTs were tested for the disintegration time (Table VII). Although DRP-ODTs showed higher tensile strength than the control, tensile strength was lower than 1 MPa for all tablets. This can be attributed to tablet matrices that contained 10% of the pellets, which enhanced mechanical properties. In addition, the results showed a possible correlation with the properties of each batch as pellets of good strength influenced ODT strength. For instance, 90 µm pellets (no compaction)

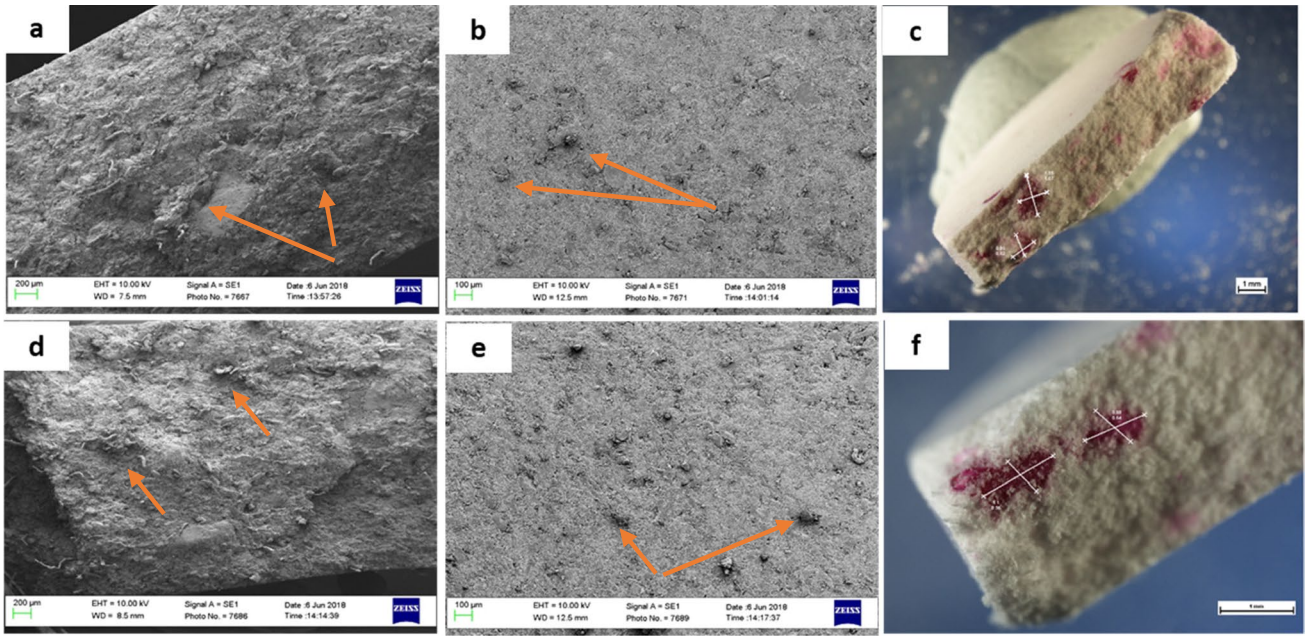



**Fig. 8** SEM and stereomicroscope images show cross-sections DRP-ODTs after hardness and the top view of the tablet indicating the embedded pellets for 63 µm batch (**a**, **b** & **c**) and 90 µm (**d**, **e**, & **f**) Arrows are annotating some of the pellets within the ODTs matrix/ on the surface

**Table VII** Relationship Between the Disintegration Time and Hardness of the Tablets with the Embedded Pellets and the Control Tablet of ODTs Matrix only

| Tablet | Tensile strength (MPa) (mean ± SD) | Disintegration time (s) (mean ± SD) |
|---|---|---|
| Control | 0.80 ± 0.060 | 20 ± 0.3 |
| 45 µm ODT | 0.87 ± 0.23 | 16.3 ± 0.5 |
| 63 µm ODT | 0.84 ± 0.03 | 14 ± 0.6 |
| 90 µm ODT | 0.89 ± 0.08 | 14 ± 0.6 |

showed the highest tensile strength. Similarly, tablets of that batch showed the highest strength. However, the 45 µm batch behaved differently and had 0.87 MPa strength tablets. The reason behind that could be the rough surfaces of 90 µm pellets allow the generation of mechanical interlocking with the particles of the ODTs matrix, leading to stronger bonds compared to pellets of smoother surfaces (45 µm & 63 µm) [63].

Nevertheless, the difference was insignificant ($p > 0.05$), and all batches were considered of good strength. Therefore, the variation within tensile strength did not affect the disintegration time as all ODTs showed fast disintegration with less than 30 s [64] (Table VII), within the specified times as recommended by the European Pharmacopeia and United states Pharmacopoeia. Moreover, the fast disintegration of DRP-ODTs can be related to the possibility of void formation between large, embedded pellets and the small particles of the matrices [65]. Hence, this could be a positive factor in providing a cushioning layer supporting the pellets' integrity under compression [66]. Therefore, the values indicated adequate mechanical strength.

## IND Release Analysis

The prepared DRP-ODTs batches were evaluated to detect IND release in acidic (pH 1.2) and buffer (pH 6.8) media using HPLC for IND to be quantified. Also, ODTs containing IND as powder were tested as a control to compare with the obtained DRP-ODTs and uncompressed pellets from all batches. All tablets were tested to evaluate IND release in dissolution media (acidic and buffer), as shown in Fig. 9.

The pellets and DRP-ODTs were assessed independently to detect IND release in acidic (Fig. 9a and b respectively) and phosphate buffer media (Fig. 9c and d respectively) using the validated HPLC method, as detailed earlier. This was applied to detect the difference between the compacted pellets within ODTs and the uncompacted pellets. The IND release for both pellets and DRP-ODTs showed a delayed release in acidic media, as shown in Fig. 9a and b, respectively. The control of IND tablets showed more than 9% within 2 h, while DRP-ODTs showed less than 2%. However, the release from 90 µm (pellets and tablets) demonstrated a consistent delay in IND release compared to those of 45 µm showing a significant difference ($p < 0.05$). However, the difference was insignificant between 90 and 63 µm in both tablets and pellets, which can be correlated with the closeness of the results of these batches, including porosity

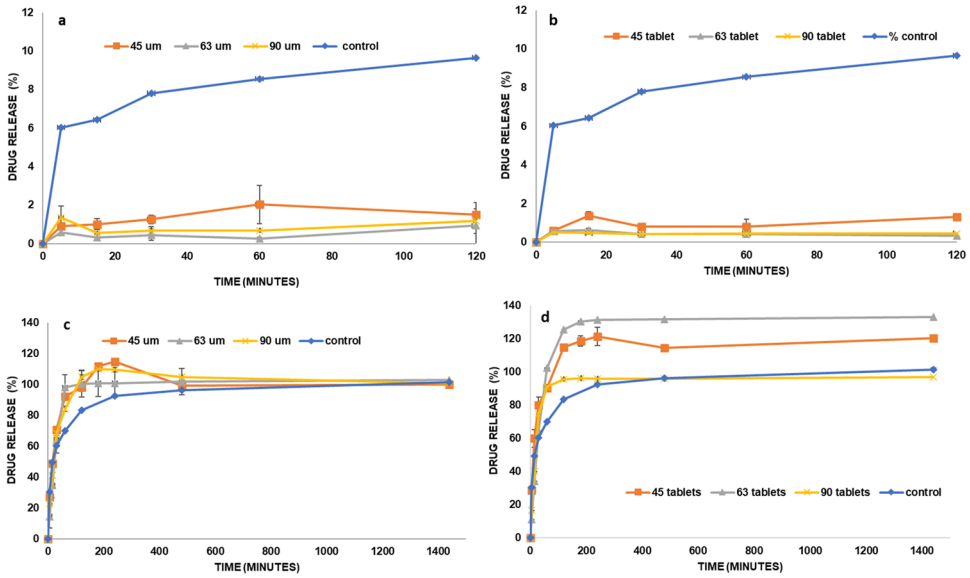



**Fig. 9** Dissolution test results of IND from pellets, DRP-ODTs in acid media pH 1.2 (**a**) & (**b**), respectively and of pellets and DRP-ODTs in buffer media pH 6.8 (**c**) & (**d**), respectively

and pellets' mechanical properties (YM and tensile strength). On the other hand, the 45 µm and 63 µm and 45 µm and 90 µm batches (tablets and pellets) showed a significant difference ($p < 0.05$) in IND release in the acidic media at 30 min. Similarly, the DRP-ODTs showed the same significant difference once between batches 45 µm and 63 µm and 45 µm with 90 µm while no remarkable difference between batches 63 µm and 90 µm of DRP-ODTs. This finding occurred due to the homogeneity resulting from pellets AR ($p > 0.05$), pore volume and powder mechanical properties of 63 µm and 90 µm. Moreover, the results indicated the good mechanical properties of the pellets as there was no significant difference in the IND release from the pellets before and after compression from each batch (45, 63 and 90 µm) within the first 30 min according to One-way ANOVA and t-test ($p > 0.05$).

Nevertheless, there was a sudden release of IND from the 45 µm pellets between 5 and 20 min and similarly in the DRP-ODTs of 45 µm (no significant difference) ($p > 0.05$). However, the second sudden release was associated only with 45 µm between 40–60 min, and this behaviour was absent in the same batch of tablets. This could be attributed to a formulation defect in the process, which did not appear in the tablets. Therefore, it can be concluded that pellets prepared from 63 µm and 90 µm showed a consistent delayed-release and good mechanical properties compared to the other batches in both non-compacted pellets and DRP-ODTS. Moreover, they offered good resistance under compression as the IND release was similar after tablet compression. Additionally, ODT disintegration time and hardness were good enough compared to other batches. As a result, the pellets of 63 and 90 µm demonstrated maintained integrity, successfully achieving the aim of the study. However, further optimization to enhance the pellets' shape and reduce pellet sizes by modulating the spheronization speed can be applied for future approaches [67].

IND release in phosphate buffer showed immediate release for all formulations with more than 60% of IND release as in Fig. 9c and d. Although the IND release was higher than 100% for DRP-ODTs, the pellets with no compaction showed consistent, immediate IND release. Hence, all pellets showed no significant difference with the control of IND tablets within 30 min in the buffer media. However, DRP-ODTs demonstrated a significant difference ($p < 0.05$) compared to the control batch in the buffer media at 120 min (2 h). There is possible segregation of powder and pellets during the tablet preparation as the particles had different sizes resulting in a higher number of pellets in the tablets than control [52]. Therefore, for optimization, the formulation granulation of the ODTs matrix or using different particle sizes could solve this issue as suggested by Tunón (2003) [52]. Hence, the excipients that are contained in the ODTs can be secondary agglomerates combined with pellets.

However, this difference did not affect the IND release in acidic media, indicating that the pellets could protect their integrity under compression and delay the IND release. Therefore, the increment of IND release in buffered media can be only attributed to the uniform particle size distribution. In addition, it was a remarkable coincidence indicating the ability of the system to protect the IND release in acidic media even there was a higher number of pellets within ODTs.

Furthermore, as shown in the DSC results, Eudragit L100 elastic properties were improved with sorbitol, which significantly helped retain the IND particles within the polymeric matrices due to the ratio of methacrylic acid and methyl methacrylate [68]. Nevertheless, the presence of

IND particles on the surfaces of the pellets and the presence of hydrophilic plasticizer could result in the sudden IND release in acid, yet this effect was minimal as the delayed release continued until the end of the test. Finally, despite the low porosity demonstrated by the pellets of higher porosity showed good compaction properties offering a consistent drug release as in 63 µm and 90 µm batches [69]. A similar trend was reported by Tunón, Gråsjö and Alderborn, showing that the pellets with low porosity were compressed with minor densification increasing the drug release. Thus, compared to non-porous pellets, porous pellets showed no change in the drug release after compression [70]. However, this finding is one of the factors that should be accompanied by the good mechanical properties of the pellets offering good compressibility and limited impact on drug release. Therefore, this confirms our statement for the necessity of demonstrating adequate elastic–plastic properties by pellets to support their integrity under compression and influentially modify the drug release. Therefore, the compacted pellets within the ODTs is expected to protect IND users from the side effects such as gastric ulcers.

## Conclusions

It can be concluded from the presented study that different factors are affecting the pellets' mechanical properties. These include initial powder particle size, mechanical properties of the powder, moisture content of the pellets, pellets' sphericity, and porosity. In addition, it was found that there is a significant relationship between the morphology and hardness of the pellets. For instance, rough surfaces tend to have higher bonding sites making the compact strong. Moreover, The batches of pellets with particle sizes of 63 µm and 90 µm exhibited beneficial effects due to their relative porosity providing enough voids to allow pellet compression with limited effect on drug release compared to the pellets of the low porosity of 45 µm. Therefore, low values of porosity demonstrated by the pellets could preferably offer a positive impact for maintaining pellet integrity under compression, thereby retaining IND release compression. Finally, the IND release was modified in the acidic media and immediately released in the buffer media showing that pellets could delay the IND release to bypass the stomach and release in the small intestine. The superior performance of 63 and 90 µm pellets suggests potential for scalability in manufacturing delayed-release ODTs for all NSAIDs, enhancing the clinical outcome for millions of chronic NSAIDS users. However, further optimization for 60 µm and 90 µm pellets is expected to be considered for future studies as this batch can be used as an anticipated formulation. Improving pellet sizes and shapes by modulating the spheronization time can be applied in future approaches.

**Authors' Contributions** Conceptualization, A.E.; methodology, A.E, N.A and M.K.; formal analysis, N.A.; investigation, N.A.; writing—original draft preparation, N.A., E.D.; writing—review and editing, R.A, E.D., A.E.; visualization, A.E., supervision, A.E., R.A, M.K. All authors have read and agreed to the published version of the manuscript.

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**Data Availability** The original data presented in this study are included in the article. Further inquiries can be directed to the corresponding authors.

## Declarations

**Conflict of Interest** The author declares no conflict of interest.



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