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FORMULATION AND EVALUATION OF FAST DISINTEGRATING PELLETS

صياغة وتقييم الحبيبات سريعة التفكك

Submitted by:

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DECLARATION

I declare that this thesis, submitted for a master's degree in Industrial Pharmaceutical Technology and titled "Formulation and evaluation of fast disintegrating pellets", has been solely the result of my work except where stated otherwise by reference or acknowledgment and has not been submitted for any other degree or professional qualification.

Signature: ……

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Date: 25.6.2022

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June 2022

Suhad A. Anabousi

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List of Abbreviations and acronyms

Abbreviation	Definition
API	Active pharmaceutical ingredient
A	Area
AR	Aspect ratio
Avg.	Average
°C	Celsius
C	Circularity
Conc.	Concentration
CCS	Croscarmellose Sodium
D	Diameter
DT	Disintegration time
FDDFs	Fast disintegrating dosage forms
E-S	Extrusion-spheronization
F. D.	Ferret diameter
Gm	Gram
hrs.	Hours
HPC	Hydroxypropyl Cellulose
HPMC	Hydroxypropylmethylcellulose
(κ)- carrageenan	Kappa carrageenan
L.O.D	Loss on drying
MC	Methylcellulose

MCC	Microcrystalline cellulose
µm	Micrometer
Mg	Milligram
Ml	Milliliter
Mm	Millimeter
min.	Minutes
MUPS	Multiunit particulates
Nm	Nanometer
Orph. Citr.	Orphenadrine citrate
%	Percentage
P	Perimeter
PEG 400	Polyethylene glycol 400
PPXL	Polyplasdone XL10
PVP	Povidone
Ps. HCl	Pseudoephedrine hydrochloride
Q	Quantity
R	Radius
RSD	Relative standard deviation
RN	Roundness
SCMC	Sodium carboxymethylcellulose
sec.	Second
S. load	Spheronization load
SQRT	Square root

STD	Standard
SD	Standard deviation
SF	Successful formulation
UPLC	Ultra performance liquid chromatography
USP	United states pharmacopeia
VF	Volumetric flask
w/w	Weight/weight

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Abstract

In the pharmaceutical industry, pellets are small spherical units with good flow-ability and are prepared by fine powder agglomeration of active pharmaceutical ingredients and suitable excipients, with many technological and therapeutic advantages. Extrusion-spheronization is the most commonly used technology to produce pellets by utilizing microcrystalline cellulose (MCC) PH 101 as a pelletization aid. Extruded-spheronized drugs with MCC, especially poorly water-soluble drugs, have the major drawback of lack of disintegration and, as a consequence, prolonged drug release.

This thesis aimed to develop fast disintegrating pellets and modulate the extended matrix-type drug release profile from MCC-based pellets. Pellets containing MCC PH 101, a filler such as mannitol, hydrophilic polymer PEG 400, and a super-disintegrant combination of polyplasdone XL 10 and croscarmellose sodium were prepared. They were then evaluated for their particle size distribution, shape, yield, moisture content, friability, and disintegration. Furthermore, two model drugs with different solubility were uploaded and evaluated, as well as dissolution profiles were studied.

In general, the findings of this investigation showed that the inclusion of soluble filler mannitol and utilizing the solubilizing power of the hydrophilic polymer PEG 400 results in a more porous matrix. This matrix facilitates water entry and the rapid swelling, complemented by the wicking effect of a combination of disintegrants, which avoids slow diffusion from the insoluble matrix of MCC pellets and could produce batches of acceptable size, sphericity, and fast disintegrating pellets.

الملخص

في صناعة المستحضرات الصيدلانية ، الحبيبات عبارة عن وحدات كروية صغيرة تتمتع بقدرة تدفق جيدة ويتم تحضيرها بواسطة تكتل مسحوق ناعم من المكونات الصيدلانية النشطة والسواغات المناسبة ، والتي تتمتع بالعديد من المزايا التكنولوجية والعلاجية. تعد تقنية البثق والتكوير هي أكثر التقنيات استخدامًا لإنتاج الكريات باستخدام السليلوز (microcrystalline cellulose) كمساعد للتكوير. إن العقاقير المبثوقة مع السليلوز، وخاصة الأدوية ضعيفة الذوبان في الماء ، لها عيب رئيسي يتمثل في نقص التفكك ، ونتيجة لذلك ، يتم إطلاق الدواء خلال فترة طويلة.

الهدف من هذه الأطروحة هو تطوير حبيبات سريعة التفكك وتعديل طريقة إطلاق الدواء من نوع المصفوفة الممتدة من الكريات المستندة إلى .MCC تم تحضير الكريات المحتوية على (microcrystalline cellulose PH 101)، سواغ مثل مانيتول ، بوليمر قابل للذوبان في الماء (polyethylene glycol 400) ، ومزيج فائق التفكك من (polyplasdone XL 10) و (croscarmellose sodium) ثم تم تقييمها لتوزيع حجم الحبيبات ، والشكل ، والمحصول ، ومحتوى الرطوبة ، والتفتت ، والتفكك. بعد ذلك ، تم تحميل وتقييم عقارين نموذجيين لهما ذوبان مختلف ، بالإضافة إلى دراسة ملفات تحلل الدواء.

أنتجت جميع الدُفعات حبيبات ذات حجم وكروية مقبولة. بشكل عام ، تظهر نتائج هذا التحقيق أن إدراج مانيتول حشو قابل للذوبان واستخدام قوة الذوبان للبوليمر المحبب (polyethylene glycol 400) ينتج عنه مصفوفة مسامية تسهل دخول الماء والانتفاخ السريع ، ويكملها تأثير الفتل من مجموعة من المفككات ، والتي تتجنب الانتشار البطيء من المصفوفة غير القابلة للذوبان لحبيبات (microcrystalline cellulose PH 101).

Chapter I: Introduction

1. Introduction

1.1. Multiunit particulates (MUPS)

The oral route remains the most favorable method of drug administration because of its convenience of application [1], pain avoidance, and reduced production costs [2]. Multiunit particulates (MUPS) include a variety of dosage forms like granules, pellets, and mini-tablets [3]. MUPS have several advantages over monolithic dosage forms, including less reliance on gastrointestinal emptying, which results in less inter-and intra-subject variation in gastrointestinal residence time and a lower likelihood of localized adverse effects [4]. Also, it has the ability to combine many incompatible drugs, as well as different release profiles, into one dosage form, which helps elderly patients by reducing the number of takings during the day [5].

1.2. Pellets:

Pellets are small spherical or semi-spherical multi-particulates having a mean diameter of 0.5 to 2 mm, consisting of fine powder of excipients and active pharmaceutical ingredient (API) [6]. Among MUPS, pellets are the most attractive form due to their several technological and pharmacological advantages. Free flow-ability, even size distribution [7], and "minimal surface to volume ratio" make them suitable for subsequent coating techniques [8], the ability to be divided into recommended dosage strengths without the need to change the process or the formula [9]. In addition to their reduced risk of dose dumping [10], improved dissolution as a consequence of their excess surface area [4]**,** and the small size of pellets permits them to pass across the pyloric sphincter into the intestine regardless of the content type of gastric component, which enhances their behavior in vivo by minimizing the time variance in gastrointestinal emptying. It’s usually designed for the oral route but has gotten used to other routes like subcutaneous and intramuscular [7]. The limitations of pellets are their high cost of manufacturing and their complicated stages of

processing [10]. Their volume per dose is frequently higher than that of tablets due to the lower bulk densities of pellets compared to compressed tablets. The specific surface area per dose is higher in smaller single-unit dosage forms, requiring more coating material to achieve coatings of the same thickness and functioning. Pellet preparation and subsequent capsule filling, as well as the compression of pellet-containing tablets, are more complicated and time-consuming than compressed tablets formed from granules or powder combinations [11]. When using microcrystalline cellulose PH 101 as a pelletization aid, and since it is water-insoluble, pellets made with it have diminished porosity, which is associated with the pellets' significant shrinkage during the drying step and thus inhibits the dissolution medium from entering the pellets, causing it to take a long time to disintegrate and drug release from the pellets to be delayed, particularly with poorly water-soluble drugs [11], [12]. Pellets are either coated or directly filled in sachets, in capsules, or compressed into tablets [10].

1.3. Fast disintegrating dosage forms (FDDFs)

Fast disintegrating dosage forms (FDDFs) entered the market in 1990 and are distinguished by their rapid oral, in vitro, and in vivo disintegration. It is characterized by ease and flexibility of administration for pediatrics, patients who complain of dysphagia, psychotic and geriatric patients [13]. It grants the goodness of life by giving a rapid onset of drug action, especially in relieving pain, cough, and anxiety [13].

The fast disintegration of pellets was attributed to the capillary network formed in the internal structure of pellets. It has all the benefits of solid dosage forms, such as handling is easy, stability is good, and the dose is accurate [14]. MUPS in an immediate-release dosage form may be easily dispersed over the GI tract [6].

Many researchers have used different approaches to achieve the fast disintegration of pellets [15]–[18]. B. Chamsai and P. Sriamornsak studied the effects of PEG 400, croscarmellose sodium, and polysorbate 80 with MCC and granulated by ethanol solution for achieving fast disintegration of indomethacin. [15]. Vervaet noticed that using polyethylene glycol 400 and hydrogenated castor oil enhanced the release rate of hydrochlorothiazide from MCC PH 101 pellets [18]. Kranz et al. studied preparing pellets with a high drug loading of 90% with immediate release properties by using only a small quantity of super disintegrant and pore former PEG 6000 [16]. Souto C and co-workers studied the effects of croscarmellose sodium and sodium starch glycolate on increasing the dissolution rate of pellets containing hydrochlorothiazide. However, only a slight increment in drug release was observed [17].

1.4. Manufacturing of pellets

1.4.1. Process and equipment

Pellets can be formed using a variety of technologies based on different principles, as shown in (Figure 1). Extrusion-spheronization and layering technologies are two of the most commonly used pelletization processes [7]. Pellet quality is influenced by various factors, including formulation, processing conditions, and equipment utilized. Parameters of the formula will affect the process and the properties of the product, such as the roughness of the surface and the porosity. Sousa et al. identified that the presence of fillers, whether soluble or not, disintegrants and surface-active agents can modify drug release [19].

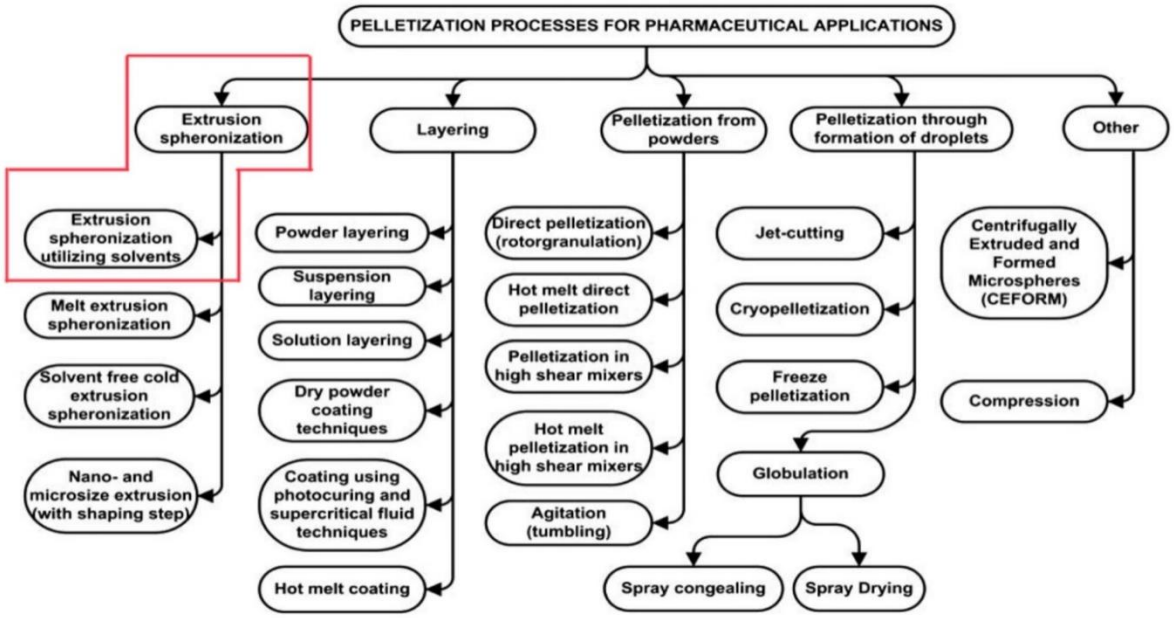


Figure 1: Technique used for pellet production [7].

1.4.1.1. Layering technology

Powder layering refers to the application of repeated layers of material over inert cores, which are commonly made of sugar or MCC [7].

1.4.1.2. Direct palletization

It enables pellet production from powders in a single device, as well as drying and maybe coating. When compared to other procedures that need many pieces of equipment, it is characterized as a quick and efficient method that can reduce the complexity and cost of multi-step pelletization, as well as the risk of cross-contamination [7].

1.4.1.3. Cryopelletization

This process employs freeze-drying techniques. A liquid nitrogen stream freezes droplets of a liquid carrier, such as a suspension, solution, or emulsion. After that, the frozen droplets are lyophilized, resulting in pellets [7].

1.4.1.4. Extrusion - spheronization (E-S)

Extrusion-spheronization (E-S) is a pelletization technique for producing pellets appropriate for immediate and controlled-release dosage forms [20]. E–S is a two-stage process in which a soft-solid material is created by combining the excipient, active pharmaceutical ingredients (APIs), and binder liquid, which is then extruded to produce rods of a specific diameter, spheronized into spherical, dense pellets, and thereafter dried or processed [21]. Because of its potential to combine numerous actives while retaining appropriate particle sizes, extrusion spheronization is the most widely used process for producing pellets. It can generate extremely spherical pellets with a narrow size and shape distribution. As a consequence, it has good flow-ability, and other processing stages like coating and compaction can be easily accomplished [7], [22]. Heilman et al. uploaded pellets with up to 80% active pharmaceutical ingredient (API) using (E-S), which could not be accomplished using other approaches [6]. It is, however, more time-consuming and labor-intensive than other techniques [6], and it is a sensitive process that is prone to failure if the formulation is subjected to minor changes [23]. The perfecting of the E-S technique necessitates good knowledge of how the paste's characteristics impact its performance during extrusion and the following spheronization stage [22]. Each stage in the process has its own set of variables that have a significant impact on the end product's quality. Furthermore, in comparison to traditional granulation, the procedure requires a large amount of water, an even distribution of the water in the wetted mass, and adequate drying conditions, which may not be ideal for moisture- and heat-labile drugs [11].

There are a variety of pellet formulas available on the market, such as Xenical® (Orlistat), Nexium® (Esomeprazole Mg), Singulair® Montelukast sodium, Cymbalta® Duloxetine, Aggrenox® (Aspirin IR, Dipyrimadole ER), and Dexedrine® (Dextroamphetamine) [20].

1.5. Extrusion spheronization (E-S) steps:

The overall process step consists of multiple unit operations, as shown in (Figures 2 & 3) [11], [24].

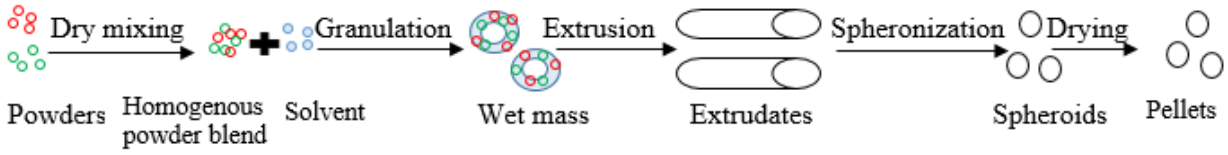


Figure 2: Stages associated with extrusion spheronization [11].

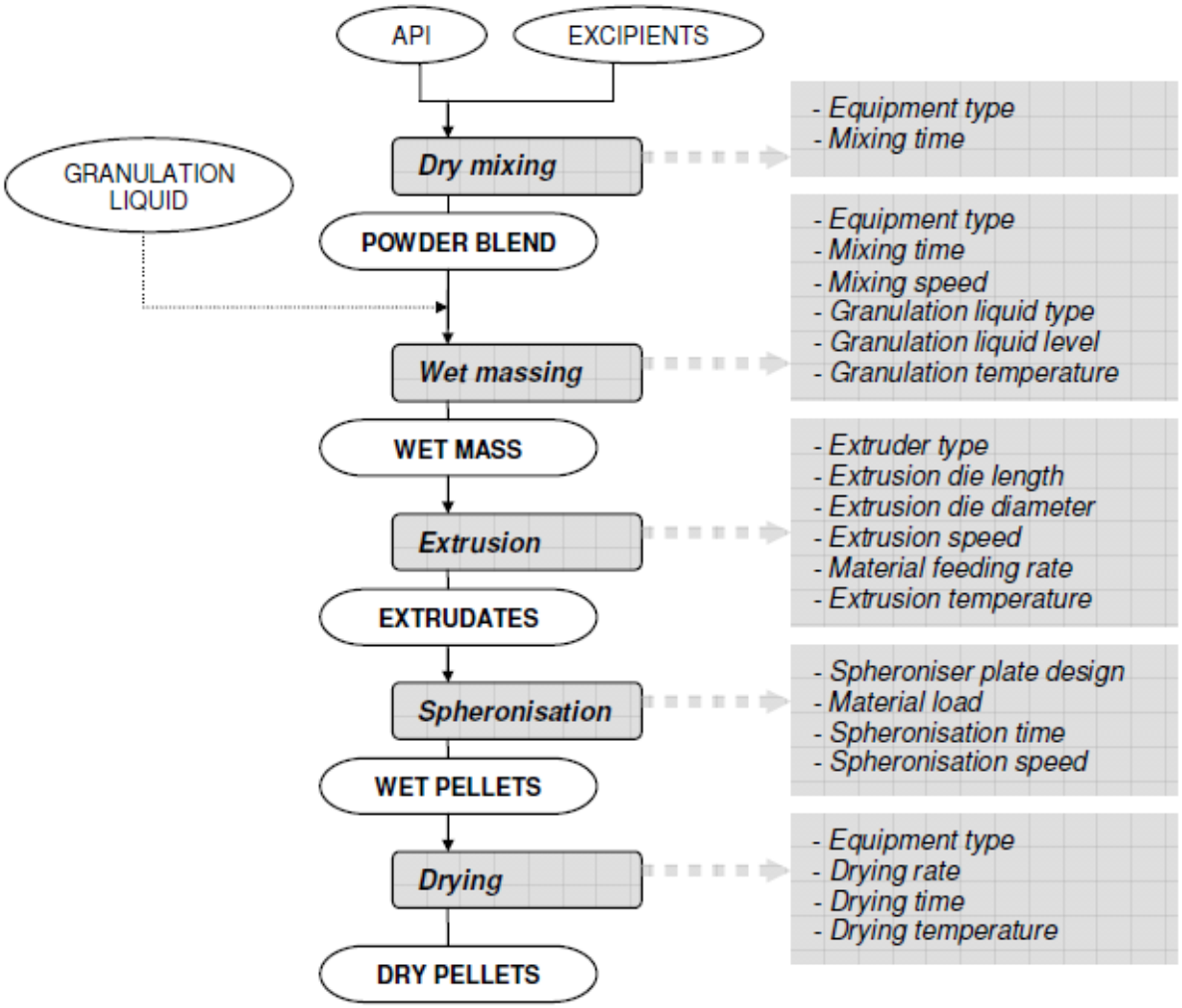


Figure 3: Flow chart for extrusion and spheronization with process parameters [24].

1.5.1. Preparation of feed

Blending the dry powder to get a compatible powder mix, wet granulation by binder solution to achieve wet plastic mass. Generally, dry mixing and wet granulation are performed in the same device (sigma blade mixer, planetary mixer, or high shear mixer) [6], [10], [25].

1.5.1.1. Dry blending

It's the first step. Here, dry powder is mixed to attain a uniform powder mix that has considerable influence on the quality of granulation and, as a result, the spherical particles produced. But differences in material properties such as size and solubility may lead to unequal distribution of materials, resulting in over-wetting. Fine and more soluble powders may dissolve and turn into granulating solvents. The solvent rich in dissolved material may continue as regions that are over wet or with a resumption of wet granulation can be re-divided. Here, the critical parameters are the type of equipment and the time of mixing [6].

1.5.1.2. Wet massing

The second phase is granulation, which involves creating a wet mass with the desired plasticity or deformation properties, so that it may be extruded and spheronized later [26]. It involves four critical mechanisms: wetting, coalescence, consolidation, and attrition. To begin, wetting is influenced by various granulation process parameters such as granulation solution addition rate, fluid distribution, and formulation property [6]. It promotes fine powder nucleation; then, in coalescence, there is a successful collision of two powder granules, resulting in a new larger granule with the establishment of strong hydrogen bonding; water gives the necessary plasticity to the mass at this stage, resulting in a permanent bond [25]. After that, the granules are consolidated by bed agitation because of compaction forces. This stage is very critical in determining the

porosity, strength, and hardness of granules and dissolution. Finally, weak granules are susceptible to attrition [6].

Wet massing is a significant parameter that should be improved before the process [5]. The equipment employed, the solvent type and quantity, and the period of wet massing are the most crucial parameters in wet granulation. The amount of granulating fluid required and the importance of obtaining a uniform dispersion of the fluid are the two primary distinctions in the granulation step when compared to ordinary granulations for compression. The volume of fluid required for extrusion-spheronization to produce uniformly sized and spherical pellets is likely to be higher than for traditional granulation for tableting [6].

In a study, researchers found that the extrusion behavior and final pellet size and shape distributions of MCC pastes were found to be unaffected by mixing duration, liquid addition rate, or mixer speed [27]. It has previously been demonstrated that the amount of granulation liquid used has a significant impact on pellet quality [28].

Varshosaz investigated the effects of varying volumes of granulating liquid and observed that employing a larger amount of solvent slowed drug release due to increased hardness. It also widened the distribution of particle sizes and lowered the pellets' friability [29]. Likewise, L. Baert noticed that when more granulation liquid was used, the release was slower. The slower rate of release was linked to an increase in the pellets’ hardness and density [28]. In addition to that, he observed that pellets with the most water granulated into them (115%) as dry weight. The result was round sphere with a smooth surface, while in pellets made with the least amount of water (75%) as dry weight, the spheres are not round and a form of folding occurred during the spheronization process [28]. Furthermore, E. Theismann observed that when the moisture content

in wet massing is reduced, brittle extrudates are created, which when spheronized produce dumbbells [30].

Also, C. Londoño studied the wet mass effect on the physical properties of pellets and concluded that a high wetness percentage was linked to a significant increase in pellets size, whereas a minimal wetting level caused the mass to be less cohesive and more prone to being destroyed by the rotating plate. For illustration, if the moisture content of the extrudate is below a certain target level, a lot of dust will be created during the spheronization phase, resulting in either higher production of fines due to extrudate attrition as it falls between the chamber wall and the spheronizer plate edge or the formation of an extrudate that, despite its length reduction, remains cylindrical or "dumbbell" pellets. On the other hand, if the moisture content exceeds a specified maximum level, an overweighed weight and aggregation of individual pellets develop as a result of excessive water accumulating on the pellet's surface. Above this point, excessive wetness produces a very sticky dough, and thus plasticity produces material that's too sticky, resulting in the formation of significantly large pellets under centrifugal force [26]. A perfect wetting degree improved mechanical strength, flow-ability, and pellet mass while decreasing pellets' friability and porosity. This suggests that the strength of pellets was inversely proportional to friability and that pellets' strength improved in pellets with larger diameters [26]. At optimum moisture content, more spherical large particles are formed as a result of simplifying the extensive creation of hydrogen bonds, thus improving the agglomeration process and thus pellet growth [26]. Also, less solvent results in finer, lower-density, and less homogeneous granules [6]. If the solvent is water, water solubility will have a significant impact on the granulation endpoint; soluble drugs may dissolve in water, while insoluble drugs may have wetting issues [6]. The amount of water requested to

achieve spherical pellets is influenced by the drug's properties. The optimal water level was lowered as the drug's water solubility increased due to the loss of the drug by solvation [30].

1.5.2. Production of pellets:

The wet mass that is going to be extruded should have a balance of deformable plasticity to allow squeezing in the extruder die to get cylindrical extrudes. Moreover, it should be strong enough to keep its shape until the spheronization process, and then it should be brittle enough to get spherical-shaped particles. It should also be rigid enough to keep itself from being destroyed by the spheronizer and have some cohesiveness to form pellets but prevent stickiness from each other [6], [10], [25].

1.5.2.1. Extrusion

The extrusion process is an essential aspect of the spheronization operation [12]. The process comprises making rod-shaped particles from the wet mass. The wet blending is obliged by pressure blades to pass through a large-diameter barrel into a smaller-diameter die [31]. During extrusion, wet mass densification occurs with shear. That induces consolidation by allowing particle-particle reconfiguration and decreasing void spaces, leading to liquids being squeezed to the surface of the extrudate, working as lubricants and smoothing the surface [32].

Researchers used various types of extruders to manage the extrudate [6], which are classified by their feed mechanism of the wet mass to the zone of extrusion into three categories: screw, gravity, and piston feed. (Figure 4) illustrates extruder types.

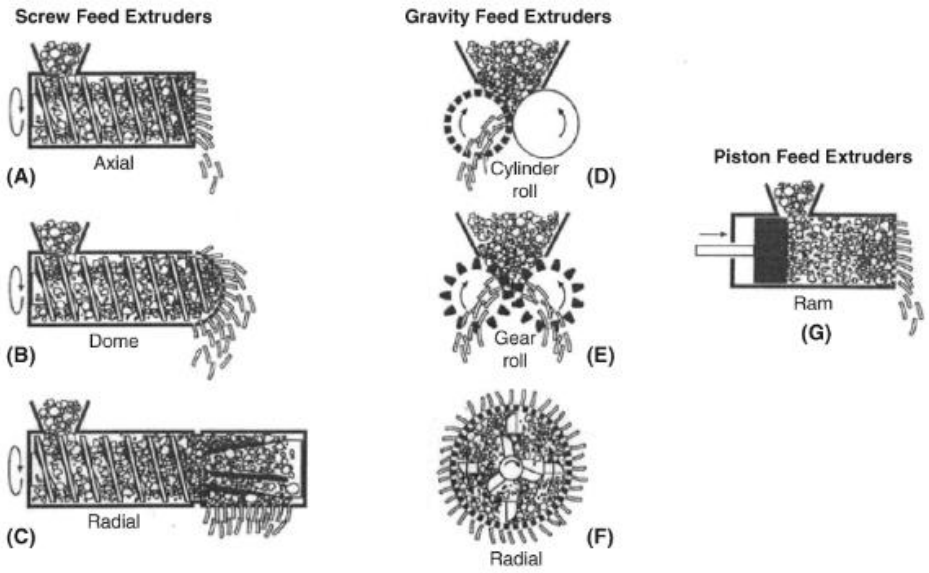


Figure 4: Extruder types [6].

1.5.2.1.1. Extrusion process parameters

Various parameters of the extrusion process that have an essential impact on extrudate and end product quality are feed rate, screw speed, screen pressure, extrusion force, orifice dimension (length and diameter), and extrusion temperature [6].

E. Theismann found that feed rate impacts pellets' roughness, yield, and moisture level, so reducing the solid feed rate leads to producing large and irregular pellets due to the high moisture content retained. That results in the extrudate sticking with each other and the formation of high-density snowballs, while a higher feed rate produces more spherical particles [30].

Several investigations have found that as *extruder speed* increases, surface defects like roughness and "shark skinning" become more evident. Because the extrudate breaks up unevenly during the early stages of the spheronization process, resulting in numerous fines and a broad particle size distribution, the surface effects of the extrudate result in lower-quality pellets [12]. While E. Theismann observed that changes in screw speed did not influence particle properties [30].

The pressure of the screen is related to the load amount, water quantity used for granulation, blend composition, and process parameters such as screen pore size and speed of the screw. A minor change in these factors impacts the pressure of the screen and, as a result, the extrusion force, which affects the yield and pellet size distribution. Sinha et al. found that screen pressure is linearly associated with the amount of water required for granulation. Increased water content decreases extrusion force. For a similar force of extrusion, it was feasible to get various outcomes when various blends of the ingredient with a specific medication were utilized or when various medications were utilized [12].

Extrusion force is exemplified by both material resistance to entering the die and material resistance to passing through the die; it depends on wet mass rheological properties [23], orifice dimension (length and diameter), and process rate [33]. So, it increases rapidly as the quantity of drugs increases and the amount of water decreases [27]. The most critical aspect is the pressure on the extrusion screen, which is dependent on the amount of water used for granulation [34].

Extrusion screen holes determine the size of final pellets [35]. As the diameter of the extrudate increases, the pellet diameter also increases [31]. The process should be optimized to ensure that extrudates will break up into pieces that have an equal diameter and length [25].

Sinha et al. studied the difference in extrudate quality by extrusion with different *screen thicknesses.* He found that the screen with the lowest thickness formed a rough and loosely bound extrudate, whereas the screen with the highest thickness formed a smooth and well-bound extrudate because of the highest densification of the wet mass in the screen with the greatest thickness. Sinha et al. concluded that the appropriate screen size is also determined by the pellets' unique size requirements [12].

Extrusion temperature management is critical when formulating thermo-labile drugs and optimizing moisture content [34]. The moisture content of the pellets is affected by the extrusion temperature. Because of the evaporation of the granulation liquid, a rise in temperature during the extrusion cycle could drastically alter the moisture content of the granules. This could lead to a variation in quality between the extrudate prepared at the start of the batch and the extrudate made at the end [12].

The variables of extrusion are less important than the quantity of granulating fluid and spheronization variables [6]. In general, water has a greater effect on final pellet size in comparison to die diameter, where resulting pellets are strongly affected by wet mass cohesiveness and plasticity [6].

1.5.2.2. Spheronization

The only stage that distinguishes the extrusion-spheronization method from traditional wet granulation is spheronization [36].

The device consists of a bowl with a static sidewall and a quickly moving grooved surface plate, which is responsible for increasing forces as particles move across it [10]. Because this plate specification determines the size of the pellet, it should be chosen with caution [35].

The friction plate utilized for extrusion-spheronization has a grooved surface to raise the frictional forces [34]. The groove design refers to the specific organization of groove lines on the surface of the plate (Figure 5) [22]. Cross-hatch geometry, in which the grooves create right angles (Figure 5b), and radial geometry (Figure 5a), in which the grooves create a radial pattern from the center, are the two common types of groove geometry. Groove edges are necessary to aid in the essential

chopping of extrudates to generate shorter, nearly uniform-length pieces [12]. In a study, they concluded that cross-hatch design produced pellets that were larger and more spherical [22].

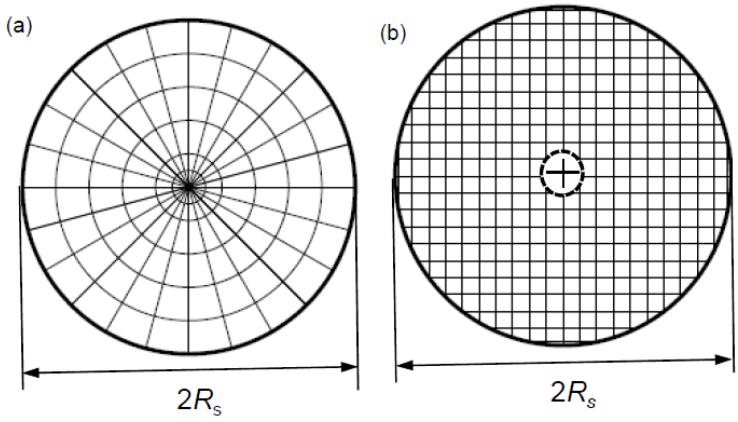


Figure 5: Radial and cross hatch design of the friction plate [22]

The design of the plate had very little impact on the tendency of the extrudates to spheronize [33]. The "cross-hatch" plate appears to be the favored friction plate (Figure 6). This is essentially a manufacturing issue, as the pattern remains the same regardless of the spheronizer plate diameter in respect of size and space of grove. On the other hand, in radial design plates (Figure 7) or striated edge plates (Figure 8), the size and space of the groove were changed as the plate diameter increased, making them more difficult to manufacture, and the frictional impacts that arises is also different, resulting in varying scale-up properties [33].

When the plate diameter increases, it was discovered that the plate's speed had to be decreased for the plate's peripheral velocity to remain constant [33].

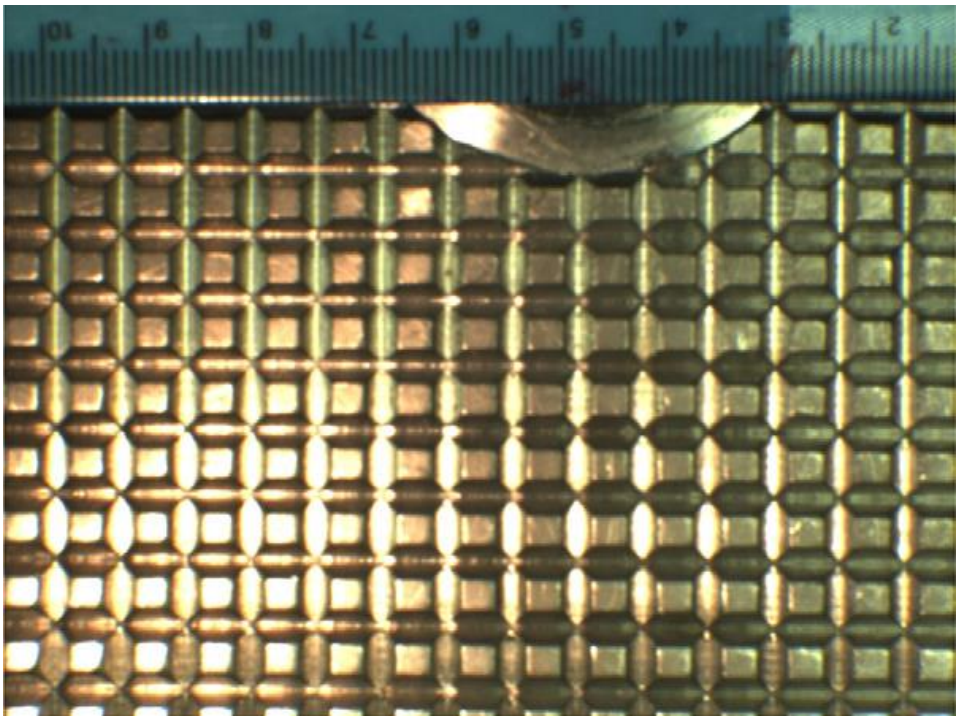


Figure 6: Cross-hatch spheronizer plate [33]

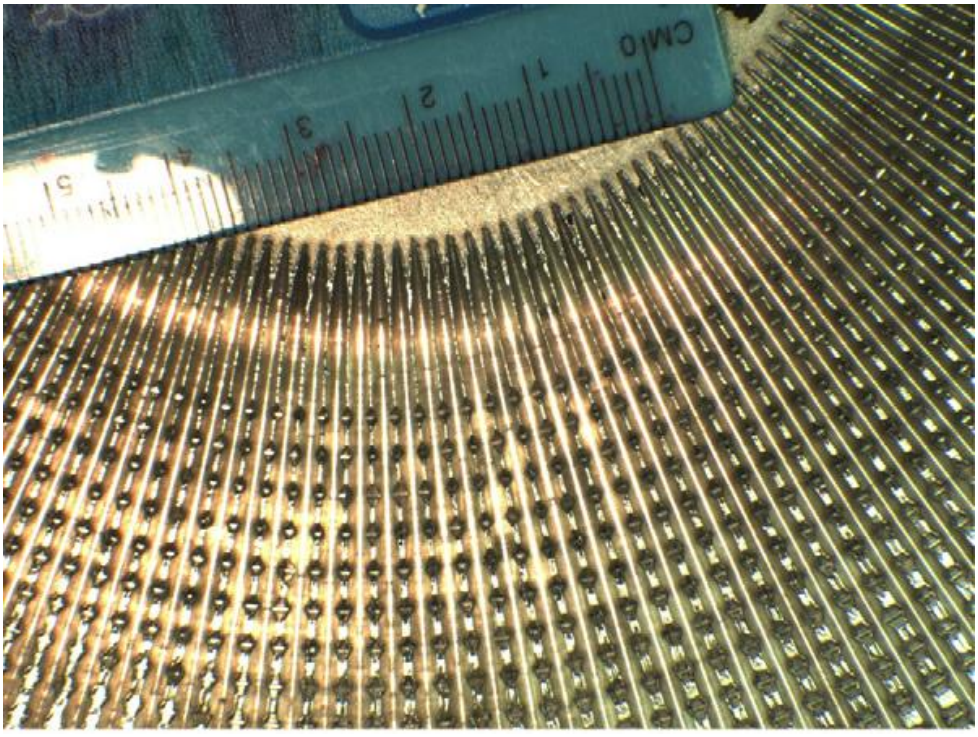


Figure 7: Radial spheronizer plate [33]

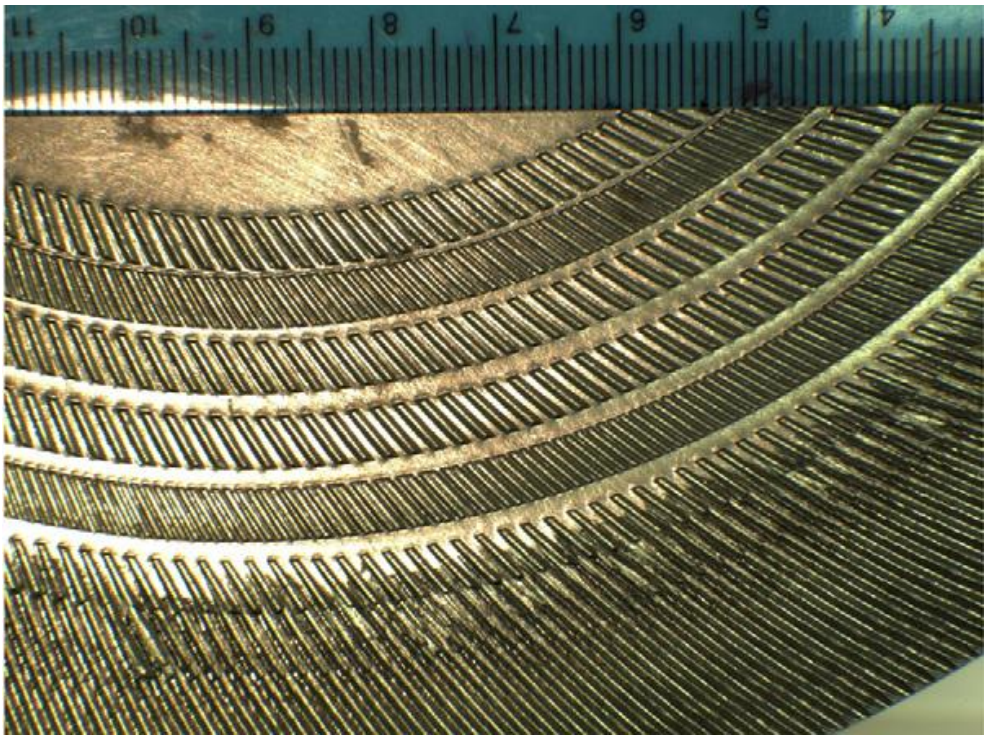


Figure 8: Striated edge spheronizer plate [33]

During the spheronization process, extrudate rounding into pellets is caused by frictional force [6]. The extrudates collide with the friction plate, the device's wall, and each other, resulting in the extrudate breaking and plastic distortion into round spheres [37].

The centrifugal force provided by plate rotation leads the extrudates to migrate rapidly towards the plate's outer rim and move in a toroidal pattern near the bowl wall during spheronization [22], producing a denser, rounder pellet [37].

A suggested mechanism of pellet formation by spheronization:

1. Some researchers propose that the spheronization process occurs in stages: The extrudate was first cut into 1.5-times-diameter lengths, which were then gradually changed into spherical pellets by length shortening and rounding them into pellets [31].
2. While Baert (1993) described the process in steps as follows: (Figure 9,1)

Cylinders distort into shapes like bent rope, and then they make dumbbells that twist in the middle. After that, the dumbbell fractures into two parts that have hollow cavities on their flat sides. Finally, the continuous collision results in the formation of spherical particles [6].

3. Rowe (1985) described the process in steps as follows: (Figure 9,2)

From a sharp cylinder edge into a rounded edge, then the particles become a shape like a dumbbell, then it turns into an ellipsoid shape, and finally, it turns into a sphere [6].

4. Also, Arbeit observed that spherical particles are also produced by mass transfer between fine particles [10].

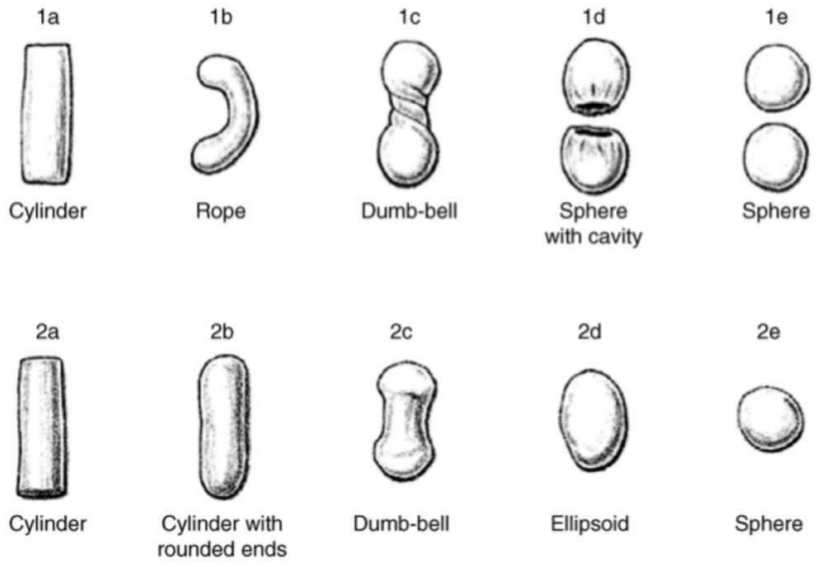


Figure 9: Spheronization mechanism [6]

1.5.2.2.1. Spheronization process parameter

Concerning spheronization stage load, speed, spheronization time, and friction plate design, they have all been proven to have a substantial impact on the spheronization performance [38].

The friction between particles and particles-plate triggers the spheronization process [30]. The plate must be loaded properly for the extrudate to be "chopped" and the fragments to rotate in a

toroidal motion. Several studies investigated the plate load effect of final pellet quality, and they observed that when the plate load is too low, there is inadequate particle-particle contact, resulting in smaller pellets with low densities and inconsistent shapes. In contrast, if the plate load is too high, the particles are unable to adequately contact the spheronizer plate, causing the production of spherical particles to take a longer time period [26], [33], [34]. However, to create spherical particles with a larger load, a longer spheronization period was required [30].

One of the most important aspects in achieving an appropriate spheronization result is moisture content [30]. The moisture content of extrudates affects spheronization success. During spheronization, an over-wetted mass forms into a lump [30]. Increasing the spheronizer load during spheronization raised the moisture content of the spheronizer chamber, preventing further water evaporation from the pellets into the environment of the chamber. A lower drop in pellet moisture level may result in more spherical pellets [12].

It has been reported that the spheronization speed must be optimized to get the appropriate particle densification, which can be inadequate at low speeds [30].

When the spheronizer speed is low, it leads to low interactions, resulting in particle rounding failure [30]. Also, at low speeds, a longer spheronization period encourages wet extrudate molecules to agglomerate with fine particles, reducing fine particle loss during spheronization [34].

Neha Shah found that primary high spheronization speed is necessary to minimize the extrude length, but if the speed is maintained, more fines are produced. Therefore, to limit fine formation and obtain spherical pellets, it was not possible to set the speed and duration of spheronization to a fixed value. Pellets were made at first at high speed, then at a medium speed, just quick enough

to round off extrudes [3]. Moreover, when the water content is low, the spheronizer speed takes priority over time [30].

Theismann noticed that, in terms of roundness, regardless of the load, higher speeds always result in more spherical particles. Low spheronization time, especially when combined with low speed, results in more dumbbell-shaped pellets. Furthermore, when combined with high speed, this effect was minimized [30].

The particle roughness was increased by the high load and by using a low speed in combination with a short rotation duration. Irregular particles were developed by a high load, while dumbbell-shaped particles were formed at a low speed. The slower the speed, the bigger the load, and the shorter the period, the fewer particle-plate interactions occur, resulting in abrasions and loss of the material [30].

For a short time, the particles with the lowest roughness were those with the highest rotation speed. The rotation speed and time had a major impact on roundness, with roughness varying based on the spheronizer load, time, speed, and solid feed rate [30].

The size was affected by spheronization speed but not the porosity [8]. When the spheronization time is reduced, larger particles are produced. The cause of this occurrence is that the particles do not have enough time to round off, and therefore "bone" shaped particles are generated during spheronization, with greater particle sizes [36].

At a high rate and time of spheronization, larger pellets are produced with a more regular shape. On the other hand, the low spheronization rate and time resulted in the development of smaller irregular particles. As a result, a sample is lost near the revolving plate's edge [26].

When pellets were formed at low spheronization rates, the size distribution was more scattered, but when pellets were formed at higher rates, the resulting pellets were bigger and had a tight size distribution. The spheronization time, otherwise, had no significant impact on the size distribution. As a result, pellet growth was determined more by spheronization rate than by spheronization time [31].

The effect of friction plate geometry and groove design has gained little interest. The impact of three groove line configurations with edge patterns that are cross-hatched, striated, and radial on pellet quality was investigated. The researchers reported that the striated edge has a good yield with pellets that have high porosity and, consequently, low mechanical strength. He ascribed the differences to the plate's frictional force magnitude on the extrudates [33]. Considering the lack of grooves, the striated edge plate is less effective in densifying pellets, and when the spheronizer load increases, frictional forces are reduced even more, producing more porous pellets. When cross-hatch or radial plate designs are used, the higher friction combined with the increased weight of the bigger load results in greater densification [33].

The influence of four cross-hatched design plates with variable shape and/or dimension of protuberance surface and a similar groove line on pellet properties (Figure 10) "(pyramidal A), (small studs B), (large studs C), and (saw-toothed D)" was investigated by M. Zhang, he concluded that the yield differences are not statistically significant. While pellets size distribution has some differences, that’s attributed to 1. The protuberances on plate C are more significant in size and spacing, and there are fewer protuberances per unit area. As a result, the collision frequency between the friction plate and the extrudates is inadequate to minimize the final pellet distribution; 2. The protuberance sizes for plates A and B are equivalent, resulting in similar mean and standard deviation values for their pellets. 3. Sharp edges at a 45° angle on a plate D with saw-toothed

protuberances may encourage cutting and thus produce smaller pellets. Pellets formed using plates A and B are spherical, while pellets made with plates C and D are less uniform. Suggesting that the magnitude of collisions and the subsequent deformation differ between the plates. There was no systematic variation in water content across the four studied plates [22].

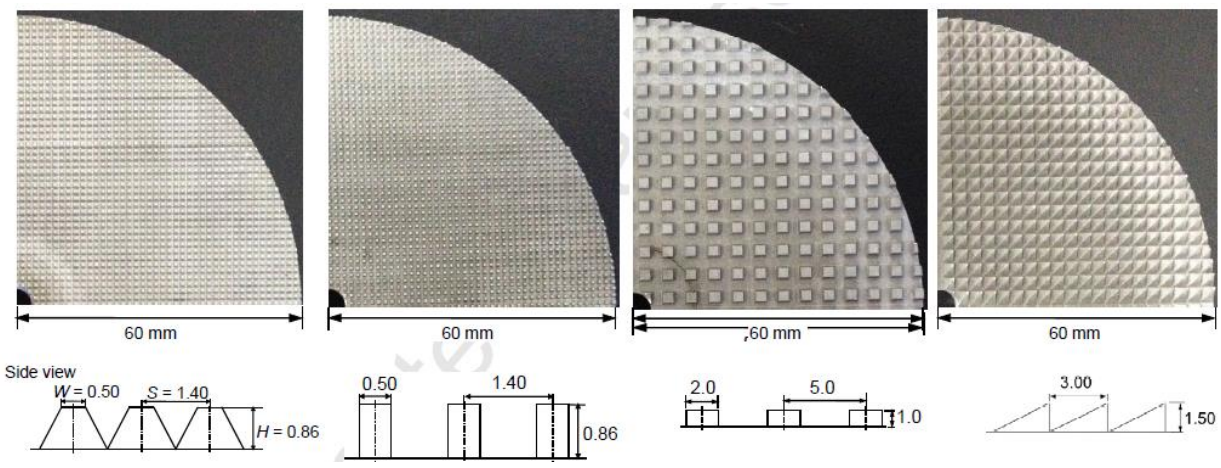


Figure 10: Pyramidal A, small studs B, large studs C, and saw-toothed D friction plates [22]

In a study, the researchers found that it is easier to spheronize formulations with a reduced proportion of drugs and low water-soluble medications [34].

1.5.3. Curing of pellets:

After that, drying the final product to attain the required moisture content and, finally, elective screening to attain the desired particle size distribution [6], [10], [25].

1.5.3.1. Drying

Drying is usually described as the removal of liquid through the use of heat and is accomplished by the transition of steam into an unsaturated state, although alternative non-thermal procedures (such as drying with moisture-removing substances) are also used. Drying techniques can be

characterized based on the mode of heat transmission or solid handling, i.e., static or dynamic system [39].

The drying temperature, as well as the drying method, can have a significant impact on pellet porosity and size [40]. Although there seems to be no shape modification when the product dries, the diameter may vary. The higher the drying temperature, the smaller the diameter, indicating a shrinking action [12].

The process of drying is determined based on the recommended particle characteristics [6]. It's the last phase, and it can be done in a variety of dryers, including ordinary hot air ovens, fluid bed dryers(FBD), freeze dryers, desiccators, and microwaves [39]. The evaporation rate of granulation liquid and how the material is managed during drying are the key distinctions between the dryers [6]. One of the key drawbacks of microwave heating is the inability to heat materials uniformly. As a result, the microwave oven may not be ideal for a uniform drying procedure because the pellets are not agitated during the drying process. Also, freeze-drying is a time-consuming and expensive process [41].

Because tray drying in a static bed is a slow process, the drug may migrate to the outer surface and re-crystallize, increasing the concentration of API at the surface and possibly increasing the dissolution rate. In FBD, as a result of the high inlet temperature and air volume, drying is a quick process [6]. Drying pellets by FBD accomplish the ideal moisture content significantly more rapidly because of the fast water evaporation and the turbulent movement of the fluidized pellets. Water evaporation from tray-dried material is delayed. Due to the bed's static nature in comparison to fluid-bed drying [34]. The drying time and temperature, as well as the type of equipment used, are critical parameters in the drying process [6].

B. Bashaiwoldu studied the effects of drying methods on pellet properties and concluded that the shape of the pellets is not affected by the drying method, while the drying method has a significant impact on the average pellet size. The overall variation in particle size was primarily related to the rate at which the pellets shrank during drying. The larger mean pellet size of the freeze-dried pellets could be due to the drying process suppressing shrinkage or, possibly, due to the pellets' swelling before drying because water expands during freezing. The mean pellet diameter of the oven-dried pellets and the pellets desiccated with silica-gel was similar but smaller. This could be due to the slow and static removal of water, which allows solid materials' shrinkage through capillary pressure due to water's high surface tension. The constant collision of pellets against each other and the wall within a fluid bed dryer did not significantly reduce the mean average diameter of pellets, owing to the short drying time, which reduced pellet shrinkage. The pellets' overall porosity increased in parallel with their mean particle size. This demonstrates that variable degrees of shrinkage and densification of the pellets occur during drying due to differences in the processes used. The rise in porosity of the pellets can be considered to be the result of a weakening of the inter-particular linkages, which is translated into a reduction in pellet strength [39].

Because MCC is a fibrous material, it can mechanically entrap water in microscopic capillaries and internal holes. Moisture flow may be hindered during the drying process because the liquid must diffuse over structural impediments caused by molecular structure [39].

Particle density was affected by drying conditions, which increased with increasing drying temperature, indicating the production of denser structures, i.e., shrinkage of the pellet during drying at higher temperatures [41].

The low dissolution rates of poorly soluble drugs resulted from the pellet's significant contraction during the drying process, resulting in reduced porosity, which prevented the dissolution medium

from entering the pellet. Increased quantities of excipient wash water-soluble drugs out of MCC pellets, leaving holes in the structure [41].

1.5.3.2. Screening

Screening may be recommended to achieve the ideal size distribution. Screening is essentially required for pellet preparation to avoid pellets with a broad size distribution[11].

1.6. Formulation

The selection of appropriate excipients is one of the most important responsibilities during formulation development [11], to ensure that the drug is delivered to the desired site, to provide the dosage forms with the desired characteristics, and to assist in the manufacturing of the drug [12]. The quality of the end product in a multi-step process is determined by the quality of intermediate products obtained after each step. The type of excipients employed has a considerable impact on each step. Extrudates that can be spheronized into pellets with acceptable particle size and specific surface properties require particular characteristics in the formulation [11].

1.6.1. Active pharmaceutical ingredients (API):

E-S technology can formulate a variety of APIs. The various drugs can be made into immediate and sustained-release pellets with a variety of uses in many fields.

The presence or absence of medication has a significant impact on the pellets' characteristics. The amount of water necessary to produce appropriate pellets, as well as the physical characteristics of the pellets, are both influenced by the properties of the drug employed. Spheronization was easier when the drug concentration was low and when water-insoluble drugs were used compared to water-soluble drugs [12].

1.6.2. Excipients

The excipients used to prepare pellets using the extrusion-spheronization technique are described in the following (Table 1) [42]:

Table 1: Commonly used excipients in pellet

Type	Examples	Function
Filler	MCC, Starch, Sucrose, Mannitol dicalcium phosphate	Make up the bulk of the material; 70 to 80 % of the excipients throughout the pelletization process [42].
Binder	Gelatin, HPC, HPMC, MC, PVP	Powder binding and maintaining pellet integrity [42].
Granulating fluid	Water, alcoholic, hydro alcoholic system	Gives the wet mass the required plasticity and cohesion [42].
Spheronization aid Pelletization aid	MCC, SCMC	Enhance pellet production by providing the plasticity and binding required for pellet integrity [42].
Lubricant	Calcium stearate, glycerin, PEG, magnesium stearate	Reduces friction between the die wall and the wet mass. They also contribute to the smooth discharge of pellets from the spheronizer [42].
Separating agent	Kaolin, talc, silicon dioxide	Materials that are adsorbed on the surface and aid in separating pellets into individual units [42].
Surfactant	Polysorbate, sodium lauryl sulfate	Lower the interfacial tension to improve wettability [42].
pH adjuster	Citrate, phosphate	To adjust the solubility of an API to fit a certain process [42].
Disintegrant	Croscarmellose sodium, sodium starch glycolate, crospovidone.	Improve drug release kinetics [42].
Release modifier	Ethyl cellulose, carnuba wax, shellac	Modify drug release profile [42].

1.7. Fast disintegrating pellets

1.7.1. Candidate ingredients for fast disintegrating pellets:

1.7.1.1. Pelletization aid

Typical palletization aid characteristics [10], [43]:

- Water-insoluble.
- Cohesive
- It has high water absorption and retention capacity, allowing it to provide the necessary rheological properties to lubricate and plasticize the surface during E-S.
- High surface area for water and excipient interaction.
- Improve the release of drugs [43].
- Significant drug loading capacity.
- No interaction with the API or excipients used.
- Produces spherical pellets with a smooth outer surface, low attrition, and high yield [10].

1.7.1.1.1. Microcrystalline cellulose (MCC)

The preparation of Microcrystalline cellulose (MCC) from cellulose by the American Viscose Company in 1962 was described by Battista, O.A., and Smith, P.A., hence the product name Avicel. The PH prefix denotes that the product is appropriate for use in pharmaceuticals [11].

MCC is a biopolymer generated from wood pulp that is used as an excipient in the manufacturing of pharmaceutical tablets and capsules [21]. It comes in a variety of grades and particle sizes. PH101 is the one most commonly used in E-S [11]. Its water retention properties, excellent binding characteristics, and high biocompatibility have earned its recognition as a "gold standard" material [21].

Due to the randomly arranged filamentous microcrystals, MCC has a high internal porosity and a wide surface area. These phenomena result in high levels of absorption and retention of moisture [26]. Furthermore, it prevents phase separation throughout E-S by controlling water movement through the plastic mass. MCC-based pellets generated via E-S exhibit high density, good sphericity with a smooth surface, and low friability [11].

Kleinebudde proposed a crystallite gel model to explain pellet generation by extrusion spheronization. He postulated that in the presence of water, MCC particles are divided into smaller particles and maybe single crystallites. Because colloidal sizes create a gel, the gel network assists E-S. As per the "sponge" hypothesis, each MCC particle behaves like a porous sponge capable of absorbing a considerable amount of water. The water would be partially squeezed out under pressure to lubricate the material during extrusion but could be returned if the pressure was released and the volume increased. While it is commonly known that MCC has unique characteristics as an extrusion aid, no model exists that adequately explains its special function. In some circumstances, the models indicated above may hold true, but not in others [8].

It's also been suggested that MCC, by auto-adhesion, increases the tensile strength of the wet mass (free cellulose polymer chains inter-diffusion). Pellets made of pure MCC that have been extruded and spheronized are rigid, non-compressible, and non-disintegrating due to auto-adhesion [11] [12].

MCC, as a spheronizing aid, has a significant impact on sphericity when combined with a granulating solvent, such as water, which functions as a plasticizer [3]; whenever the MCC proportion in the formula is increased, the holding capacity of the water prospected to be increased [27].

The MCC acts as a matrix through which the medication dissolves gradually [12]. When loading a lower API level, pelletization aid will be the most critical determinant of pellet characterization. At equal levels of API and MCC, pellets with good sphericity will be produced, but when there is high drug loading, the dissolution will be dependent on the solubility and concentration of API and excipients used. So, increasing drug solubility will increase the release rate [6].

MCC enhances significant matrix shrinkage upon the drying process, resulting in pellets with lower porosity [40]. An optimum amount of MCC was determined to grant pellet sphericity, and disintegrants were selected to improve pellet disintegration [3].

However, there are certain drawbacks to using MCC. Because MCC is water-insoluble, pellets prepared with it have reduced porosity, linked to the pellets' considerable shrinkage during the drying step, and hence prevent the dissolution medium from entering the pellets, so it takes a long time to disintegrate, and drug release from the pellets is delayed, especially with poorly water-soluble drugs [11], [12], active adsorption of some APIs like amoxicillin, famotidine, and ketotifen [16], [35], and degradation of sensitive drugs like ranitidine [43].

Other pelletization aids, according to Duki-Ott, offer less formulation flexibility as well as processing conditions [44].

Alternatives to pelletization aid for MCC

1.7.1.1.2. Pectin

Tho et al. investigated various types of pectins as pelletization aids. Because of the high degree of swelling and stickiness of the extrudates, most pectin types are not suitable as pelletization aids when granulated with pure water. Depending on the pectin type, adding chemicals like ethanol, calcium chloride, or citric acid to the pelletization process may improve the output. This was

attributed to the reduced solubility of pectin in the presence of these additives. Also, it is more sensitive to drug type and dosage. In vitro, drug release depends on pH [45].

1.7.1.1.3. Chitosan

In terms of spheronization aid properties, chitosan isn't suitable because it necessitates the inclusion of a granulation liquid with a specified pH, an additional polymer (e.g., sodium alginate, hydroxypropylmethylcellulose (HPMC), or a binder (HPMC), is needed, and ionic interactions with drugs are probable due to the ionic nature of chitosan. Chitosan's pH-dependent solubility in water is due to its cationic character: it is soluble in acidic mediums and insoluble in basic mediums [44].

1.7.1.1.4. Kappa (κ)-carrageenan

Kappa(κ)-carrageenan pellets showed an acceptable spherical shape and narrow pellet size distribution. In contrast to MCC pellets, systems based on κ-carrageenan showed fast disintegration of the pellet core, allowing for rapid drug release, irrespective of poorly water-soluble drugs. It is more robust in terms of water fluctuation. It has thermal decomposition at 70 ^{o}C, but it has limitations in possible ionic interaction and produces pellets with low mechanical stability [16].

1.7.1.1.5. Starch

Duki-Ott et al. also studied a modified starch with high-amylose as an alternative excipient to MCC in pellets with model drugs [46]. Crystalline high amylose starch has low solubility in cold water, so it doesn’t swell, it is only dispersed. Because it has a high OH group, it has a high binding with water, and its small size gives it a high surface area [47]. A binder (HPMC) was required to provide a suitable wet mass for extrusion, as is usual in starch-based pellets. Adding sorbitol

improved the surface characteristics of the pellets by altering the consistency of the wet material. He was able to achieve high pellet production with appropriate sphericity and low friability [46].

1.7.1.2. Filler

Mannitol is a commonly used diluent. It's non-hygroscopic and is useful in moisture-sensitive APIs. After wet granulation, it gives up moisture due to the negative heat of the solution [48]. It can hold 0.3g/g of water without restricting extrusion [49]. As a result of its hydrophilicity that permits better wetting of the powder with the binder, pellets of small size are obtained when using a large quantity of mannitol, especially with a small povidone concentration [4].

A. Goyanes studied using mannitol in hydrochlorothiazide pellets and observed that mannitol has a satisfactory effect on pellet morphology and enhances drug release because of its high solubility and ability to create pores in pellets when dissolved [50]. The concentration of mannitol increased the rate of drug dissolution from the pellets substantially, also producing pellets that have a small size [4].

1.7.1.3. Binder

During pelletization, the choice of an appropriate binder and its concentration, either alone or in combination with the granulating liquid, has a significant impact on pellet properties, and it is a crucial formulation variable. The binder is commonly applied as a liquid during wet massing for granulation. The liquid bridges initially bind the particles together, but as the liquid evaporates, the binder precipitation and hardening take over as the primary bonding forces [12].

A binder is usually used to enhance pellet strength and decrease the number of fines produced. But if its quantity is increased, it will produce hard pellets [25].

To exclude microbial contamination and lot-to-lot variation, synthetic polymers are preferred over natural ones [48].

Povidone (PVP) is the most commonly used binder in granulation. It's soluble in water and freely soluble in polar organic solvents, a very hygroscopic polymer. It is capable of picking up moisture even when the environment is low in humidity. PVP is found in various molecular weights. Low and medium MW are usually used, but high MW is less often because of the impeding dissolution profile. It’s used at a concentration of (0.5–5) %. Water and alcohol, such as ethanol, are used as binder activators or distributors by forming a solution or suspension. Or it may be combined in the dry state and activated during granulation by water or alcohol, but in this case, a higher quantity of binder is needed to obtain the same binder functionality as the solution [6], [48].

Pellet friability and disintegration were significantly affected by the binder. Its range was determined by the creation of a minimum proportion of fines during spheronization and the amount of disintegrant [3].

Varshosaz investigated the effects of varying PVP percentages and concluded that adding a higher percentage of binder slowed drug release due to increased hardness. It also widened the distribution of particle sizes and lowered the pellets' friability [29].

Ibrahim et al. found that by utilizing a lower PVP content, a quick wetting of the powder with the binder solution was achieved [4].

1.7.1.4. Granulating liquid

Pellet production by extrusion Spheronization is unachievable without a suitable wetting liquid, which helps to make liquid bridges between materials and gives the formulation suitable

rheological characteristics, allowing the mass to be extruded through the screen of the extruder and turned into spherical pellets [12].

Granulating liquid moves quicker than solids when exposed to the extruder force, so it will be found on the particle surface, acting as a lubricant that reduces extrusion shear force and aids in the figuration of cylindrical extrudates. Simultaneously, the existing liquid in the extrudate acts as a plasticizer, giving the extrudate a less rigid structure during spheronization. But if the phase separation is too great, this process will not succeed and a "shark-skinned" extrudate will be produced [49].

The composition of the granulation liquid has a significant impact on the structure of pellets. Shah and colleagues observed that pellets made with a 40% 2-propanol/water mixture granulating liquid had a faster dissolution rate than those made with a lesser proportion of 2-propanol in the mixture, which was due to the pellets' rapid and complete disintegration. Pellet strength decreased and a less uniform shape was produced as the 2-propranolol level in the ethanol/water fluid increased due to an alteration in the particle bonding of the pellets. MCC could not be formed into pellets using 100% alcohol [12].

M. Ibrahim and co-workers studied the effects of using co-solvents such as PEG 400, propylene glycol, and ethanol in different concentrations and noticed that the drug release rate of indomethacin increased with a 60% co-solvent concentration. They attributed the improvement to drug solubilization in the co-solvent [51].

Another study by C. Vervaet employed PEG 400 and hydrogenated castor oil. At 32% PEG, they ensure that hydrochlorothiazide is completely dissolved and the drug release reaches 80% [18].

Water

Water can be deemed as a particular condition of a film binder. Water acts as a solvent for soluble material by dissolving the particle surface, and after drying, re-crystallization occurs between the boundaries of the particle, leading to the formation of a solid bridge. Moreover, water softens the particle surface of insoluble material by coalescence because of its surface tension, leading to a plastic surface that can influence more growth. Water also encourages van der Waals forces by enhancing the true contact area of the particles [52].

The level of granulation liquid required is obviously determined by the proportion of MCC in the formulation. As the MCC fraction increased, higher water quantities were needed for optimum palletization, producing pellets of lower size and porosity [8].

Water is the most critical formulation parameter. The amount of water that must be added to the MCC for the formulation to operate properly varies. Two ultimate that may be identified. A minimum rate when the wet blend is too dry. This causes either extrudate attrition, causing it to fall between the spheronizer plate's edges or an extrudate that, despite being shorter in length, stays as cylinders or "non-rounded" pellets. While at a high rate, once chopped and rounded, the pellets quickly agglomerate [53]. The formulas with the least amount of water were the least spherical [31].

The amount of water required to make ideal formulations was also linked to the drug's solubility [53]. An increment in the solubility of the model medication coincides with a lessening in the amount of water needed. This could be clarified by a decrease in solid mass due to the model drug's solvation, allowing more water to enter the MCC sponge [53]. With an increase in the log of the

drug solubility, the amount of water necessary to make the perfect spheres decreased in a linear manner [12].

Pelletization success or failure is solely determined by the particle's ability to retain moisture within strict limits [52]. The presence of water as a granulating fluid, even in very small amounts, is the most important formulation requirement for spheronizing MCC. Once the water content in the pellets was higher, they were less friable [12].

Granulation of MCC by purified water usually produces denser pellets with high hardness and controlled release dissolution, but substitution of a proportion of water with alcohol will lower the friability and mechanical strength in addition to enhancing the dissolution profile of the pellets [54].

During extrusion, the remaining water molecules serve as lubricants, and during spheronization, they determine the morphology of the pellet [26]. As the amount of water applied increased, the force required to extrude the wet mass during extrusion decreased. The overall reduction of a consistent state of extrusion force with increasing moisture content can be attributed to reduced friction between wet powder mass particles and between the powder plug and the die wall [29].

1.7.1.5. Disintegrant

Polyplasdone is a water-insoluble synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidinone. It is found in different particle sizes in three grades. The coarser grade is called Polyplasdone® XL, while the finer grades are called Polyplasdone® XL 10 (PPXL) and Polyplasdone® INF 10. It’s a disintegrant normally used at a concentration of (2-5) %. It has good hydration ability and elevated capillary efficiency by wicking with little swelling effect [55].

In a study, Satishkumar P. Jain used PPXL as a palletization aid and postulated the mechanism as follows: PPXL will take up an added amount of water and that will form a hydration coat around the particles. As the amount of added water increases, it will progressively fill and saturate interior pores. PPXL acts as a reservoir for water because of its cross-linked structure, so it works like MCC, except hydrogen bonding ability is lower than MCC because of mechanical interlocking deficiency, which leads to increased water needed to achieve binding features. He found that PPXL was proven to be a good extrusion–spheronization aid for making melt-in-mouth pellets. PPXL-based pellets disintegrate after only a short period of exposure to liquid [56].

V. Kunam and co-workers studied using crospovidone to produce fast disintegrating pellets and noticed that it increased the dissolution of Ezetimibe 1-2 fold compared to the marketed conventional dosage forms [57].

Croscarmellose Sodium (CCS) is a polymer of modified glucose that is composed of carboxymethyl sodium [40], which has a quick-wicking and swelling ability to enhance disintegration. It's used at a concentration of (0.5–25)% [55].

H. Kranz noticed that CCS swells when in contact with water. As a result, more water is required during the pelletization process. And the drug release rate from MCC pellets was increased by using a low percentage of CCS [16].

Hadi Afrasiabi and colleagues use CCS in conjunction with PEG and find that it has a significant impact on increasing dissolution rate, which they attribute to the increased pores in the inert matrix caused by the presence of soluble PEG and the increased surface area of pellets, in addition to the presence of disintegrant [5].

The super-disintegrant CCS affected friability and time of disintegration. Swelling of CCS was detected during granulation of the dry blend, and it was directly related to the amount of CCS employed in the formulation. Regardless of binder concentration, the higher the proportion of CCS employed, the larger the swelling, which ultimately resulted in the creation of more fines upon spheronization. Sphericity is oppositely influenced by CCS [3]. CCS raises the formulation's hydrostatic pressure, inducing swelling and water wicking. These components encourage pellet swelling upon wetting, resulting in quick core destruction [40].

1.7.1.6. Pore-forming agent

Pore former is usually a water-soluble excipient that is mixed into the formula. When contacting water, it dissolves and creates pores at the surface of pellets through which the API release occurs [5].

1.7.1.6.1. Polyethylene glycol (PEG)

PEG is an amorphous synthetic water-soluble polymer that is hydrophilic and includes nonpolar moieties. It has a low melting point and is found in various molecular weights, being liquid at the lower weight and solid or semisolid at the higher. It gives plasticity to granules. It’s also used as an anticaking agent, which prevents the formation of lumps during granulation [55].

PEG has an evident effect on pellet size. The size of pellets increases with increasing PEG concentration [51].

C. Vervaet found that MCC can tolerate up to 43% (w/w) of PEG 400 and will be free-flowing. At a higher concentration, the pellets will be attached to each other. Also, he noticed that the presence of solubilizing PEG 400 is a promising excipient to enhance the dissolution of poorly soluble drugs [18].

Increasing the PEG concentration results in lower wet mass consistency, which allows for easier extrusion and the creation of smoother surfaces in the pellet [4].

M.Ibrahim studied the effects of PEG of different grades with different concentrations and observed that adding PEG resulted in producing pellets that were almost rounded and intact in shape, compared to avicel-alone pellets that were not totally spherical. The roughness of the pellet surface increased as the molecular weight of PEG increased. The medication release rate was shown to be improved by using PEG. Also, he revealed that altering the molecular weight of PEG can influence the release of drugs from matrix pellets. A significant quick-release rate was noticed when the PEG amount in the pellet formulation was increased. However, the improvement in drug release was lower with increased PEG molecular weight [58].

1.7.1.7. Model drug

The developed formula will be tested by using two model drugs with different degrees of solubility: pseudoephedrine hydrochloride, which is freely soluble in water [59], classified as class III [60], and orphenadrine citrate, which is sparingly soluble in water [61], classified as class I [60].

1.7.1.7.1. Pseudoephedrine hydrochloride

Pseudoephedrine, a common decongestant, is a sympathomimetic drug that primarily affects adrenergic receptors. The chemical formula for pseudoephedrine hydrochloride (Ps. HCl) is "(1S,2S)-2-(methylamino)-1-phenylpropane-1-ol; hydrochloride." (Figure 11) [59]. Pseudoephedrine hydrochloride is a powder with a faint odor that comes in fine white to off-white crystals [62]. The molecular weight is 201.7 and the melting point is 182.5–183.5ºC [63].

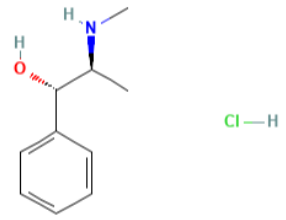


Figure 11: Pseudoephedrine hydrochloride structure [59]

Pseudoephedrine hydrochloride solubility in literature, to determine the solubility, the researcher investigated the equilibrium solubility using the shake flask method, in which excess amounts of pseudoephedrine were added to glass vials containing various buffers. After adding the drug to the buffer, the pH of the solution was checked. The vials were firmly sealed and placed in a water bath at 37°C or 25°C, shaking (100 rpm). A comparison of 48- and 72-hour samples supported the establishment of equilibrium. The vials were centrifuged (10,000 rpm for 10 minutes) before sampling, and the supernatant was carefully removed and immediately analyzed by Ultra Performance Liquid Chromatography (UPLC). The solubility of pseudoephedrine at 37°C and room temperature for the three pH values of 1.0, 4.5, and 7.5 is shown in (Table 2) [59]. The solubility of pseudoephedrine in various solutions is shown in (Table 3) [63].

Table 2: The solubility of pseudoephedrine hydrochloride in various solutions at 37°C and room temperature (25°C)[59], [62]

Pseudoephedrine hydrochloride in:	pH	Solubility at 37°C	Solubility at 25°C
Phosphate buffer	pH 7.5	835±33 (mg/ml)	428±2 (mg/ml)
Acetate buffer	pH 4.5	743±18 (mg/ml)	250±1 (mg/ml)
Maleate buffer	pH 1.0	700±9 (mg/ml)	213±1 (mg/ml)

Table 3: The solubility of pseudoephedrine hydrochloride in various solutions at room temperature (25°C) [63]

Pseudoephedrine hydrochloride in:	Solubility at 25°C	Description
Chloroform	0.011 (gm/ml)	Sparingly soluble
Ether	$1.4 * 10^{-4}$ (gm/ml)	Very slightly soluble
Methanol	0.278 (gm/ml)	Freely soluble
Water	2 (gm/ml)	Freely soluble

1.7.1.7.2. Orphenadrine citrate

Orphenadrine citrate (Orph. Citr.) is a muscle relaxant chemically "N, N-dimethyl-2-[(2-methylphenyl)-phenylmethoxy] ethanamine; 2 hydroxypropane-1,2,3-tricarboxylic acid." (Figure 12) Orphenadrine citrate is a crystalline powder that is white or almost white in color [64]. It has a melting point of 134 to 138 °C and should be stored in airtight, light-resistant containers [65].

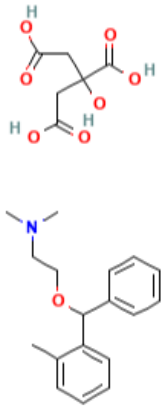


Figure 12: Orphenadrine citrate structure [64]

Orphenadrine citrate solubility in literature, to investigate the solubility of orphenadrine citrate in water and at different pH levels, the researchers added orphenadrine citrate in excess amounts to separate vials containing several media, as shown in (Table 4):

To remove any excess orphenadrine, the researcher shook each vial, sonicated it for 10 minutes, and filtered it through a 0.45µm filter membrane. The amount of soluble orphenadrine citrate in a clear solution containing orphenadrine citrate was then determined using spectrophotometry [66].

Table 4: At 20°C, the solubility of orphenadrine citrate in various solutions [66].

Media	Orphenadrine citrate in:	Solubility g/100 ml
0.1 N HCl		0.00061g/ml.
Potassium dihydrogen phosphate	Buffer pH = 7.4	2.43
Potassium dihydrogen phosphate	Buffer pH = 6	1.63l
Potassium dihydrogen phosphate	Buffer pH = 5	1.39
Water	Water	1.5

The researcher observed that as the pH of the solution increased, the solubility of orphenadrine citrate also increased; the maximum solubility was obtained at pH 7.4, which is 2.43 g/100 ml [66]. Orphenadrine is soluble at 1 gm in 70 ml of water or 400 ml of alcohol [67], slightly soluble in ethanol, and practically insoluble in chloroform and ether [67].

1.8. Evaluation of pellets

Various tests are used to evaluate the final pellet properties produced by E-S [11].

1.8.1. Size analysis

Pellets' mean particle size is an essential characteristic that is frequently utilized as a dependent variable in pellet optimization studies involving E-S. It's usually done by a sieve shaker with a series of standard sieves. The extrusion screen, spheronization time and speed, drying method, and temperature are all process variables that determine particle size. Moisture content, binder type, and concentration, and excipients are among the formulation variables that have been observed to influence pellet characteristics [12]. Pellets should have a narrow particle size distribution [11].

1.8.2. Pellet shape analysis

A variety of shapes aspect can be collected from image analysis and utilized to examine pellet shapes [32]. The license-free software Image J® is used to determine the projected area, perimeter,

Feret diameter, circularity, aspect ratio (AR) roundness, solidity, and sphericity from microscopic images, with aspect ratio and roundness being the most effective determining tools [26], [32]. The shape of the pellets should be uniformly spherical [11].

1.8.3. Friability

It's a test of a pellet's capacity to withstand shock without crashing. It assesses the pellet's susceptibility to flake off during handling, resulting in dust production [26]. Friability of pellets can be defined by one of several methods by utilizing different devices. The most commonly used device is tablet rotating drums, but as a result of their small weight and electrostatic charge, it doesn't apply appropriate mechanical stress, so to overcome this hindrance, glass or steel beads were used. Test conditions may vary from using 10 to 200 beads, the mass of pellets may be 5 or 10 gm, the testing time from 3 to 10 minutes, and the rotation speed of the device is 20 or 36 RPM [68]. It's a critical parameter to consider because pellets that are friable create fines, and the surface becomes rough [69].

1.8.4. Disintegration time (DT)

It's a crucial characteristic for fast disintegrating pellets, and it's tested using a tablet USP disintegration apparatus [42].

1.8.5. Dissolution

The dissolution test is a key component of both drug development and quality assessment. A specific, reproducible dissolution profile is essential for predictable API bioavailability [32]. These tests were carried out in tablet USP dissolution apparatus to investigate the release characteristics of various formulations to establish a link between in vitro release and in vivo absorption for pellets. The polymer and binder used, the drug's aqueous solubility, and the inclusion of additives such as surfactants all influence drug release profiles from pellets [42].

Chapter II: Objective and importance

2. Objective and importance

2.1. Importance of the study

Multi-particulate dosage forms disperse more evenly in the gastrointestinal tract, leading to improved drug absorption and reduced mucosal irritation caused by high local concentrations of some active ingredients in monolithic dosage forms [4]. The more homogenous and, to some extent, more consistent gastric emptying of pellets was related to little influence on upper intestine transit time and lower inter-and intra-subject variation of drug plasma concentration [7]. Furthermore, the ability to make dosage forms with multiple drug strengths from the same pellet batch by simply changing the capsule fill weight and the feasibility of combining various incompatible active ingredients in one product makes these systems alluring to pharmaceutical manufacturers [24].

Extrusion and spheronization have distinct advantages over most other pellet production methods in terms of robustness, low costs, and good product quality [20].

MCC has been the most attractive pelletization excipient employed in the extrusion/spheronization process to develop pellets for pharmaceutical purposes. Due to its superior water uptake capacity, water-holding ability, ideal rheological qualities, plasticity, and cohesiveness [70]. Despite all of its excellent properties, drawbacks related to the use of MCC have also been noted. The most common disadvantage is a delayed or inadequate drug release profile caused by a lack of disintegration as the pellet shrinks greatly during the drying process, specifically when used in high doses with a poorly soluble medication. This property restricts the use of MCC in immediate-release dosage forms [70].

Many Strategies to get fast disintegrating MCC-based pellets were used, such as promoting pellet disintegration by incorporation of super-disintegrant and addition of soluble filler [70], increasing pellet porosity by changing granulating liquid, modulating drying conditions, and incorporation of pore former [70]. Also partial substitution of MCC by: soluble filler retains the advantages of MCC while adding functional quality provided by the additional components [70].

2.2. Objectives

- Selecting the best compatible excipient that creates pores in the bulk of pellets to increase disintegration and, as a consequence, increase release rate.
- Developing fast-disintegrating placebo pellets.
- Loading of pseudoephedrine hydrochloride as freely soluble and orphenadrine citrate as sparingly soluble model drugs in the placebo formulation.
- Developing a calibration curve for accurate determination of each API by UV analysis.
- Studying physical properties (size, shape, and size distribution) of final pellets formulations.
- Studying the disintegration time of each API.
- Studying the release profile from each batch by the USP dissolution apparatus II.

Chapter III: Research Methodology

3. Research methodology

This chapter deals with formulation materials, tools and equipment, manufacturing procedures, and pellet evaluation techniques.

3.1. Formulation materials, tools, and equipment

All materials that were used in this research are listed in (Table 5). All materials were provided by Jerusalem Pharmaceuticals Co., Ltd.

Table 5: Lists the materials used in formulation trials and their functions.

No.	Ingredient's name	Lot. No.	Function
1	Microcrystalline cellulose PH101		Pelletization aid
2	Mannitol		Filler
3	Polyethylene glycol 400	YY00I2R501	Pore former
4	Croscarmellose sodium	201803278	Disintegrant
5	Polyplasdone XL 10®	RN537	Disintegrant
6	Polyvinylpyrrolidone K30		Binder
7	Pseudoephedrine hydrochloride	201907079	Active ingredient
8	Orphenadrine citrate	202003001	Active ingredient
9	Purified water /RO-water treatment system		Granulating liquid

3.2. Tools and equipment

All of the equipment and tools that were used in the analysis and formulation are listed in (Table 6).

Table 6: Equipment and tools required for the experiment.

No.	Equipment, tool name	Usage	Model and manufacturer
1	Easy mix mixer	Dry mixing and wet massing	Molineux, France
2	Modified HV8 food grinder	Extrusion	Molineux, France
3	Modified coffee grinder	Spheronization	Molineux, France
4	Tray oven dryer	Drying	Beko®, Turkey
5	Retsch sieve shaker	Sieving	AS200 Retsch, Germany
6	Precision balance	Weighing	PRB003 Ae adam , USA
7	Pocket scale balance	Weighing	China
8	Analytical balance	Weighing	ANB001 OHAUS®, Switzerland
9	Friability tester	Friability test	FRT012 Pharma test, Germany
10	Moisture analyzer	Moisture content test	MB45 OHAUS®, Switzerland
11	USP tablet disintegration apparatus	Disintegration test	Pharma test, Germany
12	Amber glass volumetric flask	UV analysis test	Duran, Germany
13	Glass volumetric flask	UV analysis test	Duran, Germany
14	Bath sonicator	Solubilization	BAS008 Elmasonic, Germany
15	USP II dissolution apparatus	Dissolution test	DT70 Pharma test, Germany
16	UV-Visible double beam spectrophotometer	Analysis test	UVS035 PerkinElmer, Canada
17	USB digital microscope	Size and shape analysis	RoHS, China
18	Pipette	Analysis	Samih Darwazah institute
19	Pipette filler	Analysis	
20	Beakers different volumes	Formulation	
21	Thermo scientific hot plate	Heating	
22	Plastic droppers	Formulation	
23	Plastic dishes	Formulation	
24	Needles	Binder solvent addition	
25	Sieves 300µm	Modify disintegration cell	
26	Foil plate	Drying	
27	Mortar and pestle	Pellets crushing	

3.3. Equipment

Due to high machine costs, extrusion spheronization technology is not available at our laboratories. Therefore, we designed an extruder and a spheronizer prototype by modifying a food grinder and a coffee grinder, respectively.

3.3.1. Mixing by Molineux hand mixer

A Molineux hand mixer, 200 watts, with a 500 ml glass bottle (Figure 13), were used to prepare the dry powder blend and the wet mass. To achieve low speed, a motor speed controller with 220 V 2000 W was installed to control the speed of the instrument (Figure 14).

Figure 13: Molineux easy mix mixer

Figure 14: Motor speed controller

3.3.2. Extruder configuration

To mimic the functionality of a lab-scale single axial screw extruder, the Molineux food grinder screen was substituted by a screen with a 1 mm die diameter and a 3 mm thickness fabricated from

304 stainless steel. Cold welding material was used to fill the housing slot to increase the pressure on the wet mass and reduce a material loss (Figures 15 & 16).

The grinder conveys the material (supplied manually at a consistent rate) by an Archimedes screw towards a perforated screen using the impact of a rotating auger. A cross-shaped blade, in conjunction with the plate, which spins with the auger, forces the material through the perforations.

Figure 15: Modified Molineux food grinder

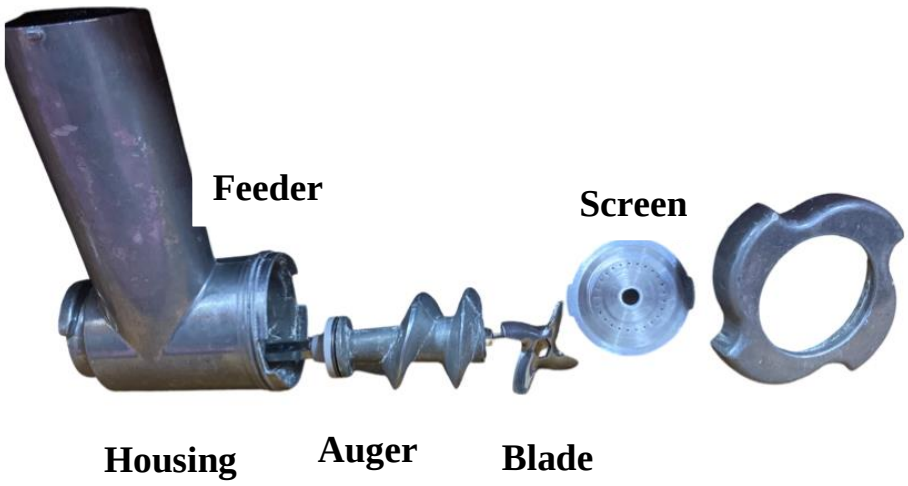


Figure 16: Wider view of modified Molineux food grinder

3.3.3. Spheronizer configuration

To resemble the functionality of a lab-scale cross-hatch spheronizer, the Molineux coffee grinder blade was substituted by a 3D printed cross-hatch plate fabricated from resins with a thickness of 2 mm and a diameter of 8.5 cm (Figures 17 & 18). Also here, a motor speed controller with a 220 V, 2000 W output was installed to control the speed of the instrument.

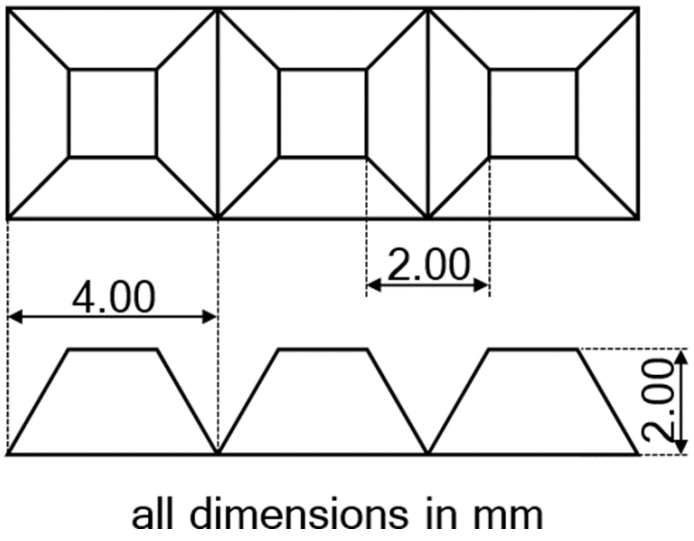


Figure 17: Friction plate dimension

Figure 18: Cross-hatch spheronizer plate

3.4. Methods

3.4.1. UV analysis

Development of an appropriate spectrophotometric method for pseudoephedrine hydrochloride and orphenadrine citrate pellet drug content and dissolution study.

A calibration curve was constructed for each API. Its concentration range was selected to cover API dissolution. Water was used as a diluent.

- Material

Pseudoephedrine hydrochloride and orphenadrine citrate standards were provided by Jerusalem Pharmaceuticals Co., Ltd.

I. Stock solution preparation:

A stock solution was prepared to obtain several standards by serial dilutions.

40 mg of each API standard was dissolved in a 200 ml volumetric flask (VF) of purified water and sonicated for 15 minutes to ensure total dissolving. Following that, 5 ml of the solution was diluted

with water in a 100 ml VF. Also, for blank sample preparation, 40 mg of crushed placebo pellets were dissolved in a 200 ml volumetric flask (VF) of purified water and sonicated for 15 minutes to ensure total dissolving. Following that, 5 ml of the solution was diluted with water in a 100 ml VF.

II. Standard solution preparation

Standard (STD) solutions were prepared by stock solution dilution. All of them were diluted with purified water.

The concentrations of STDs were estimated by multiplying by the appropriate dilution factor. Using STDs, a calibration curve in the range of 0.005-0.04 mg/ml for pseudoephedrine hydrochloride and in the range of 0.003-0.02 mg/ml for orphenadrine citrate was constructed.

III. UV analysis method

The UV analysis method is based on a USP validated method.

i) Orphenadrine citrate calibration curve

The spectrometer was auto-zeroed at 210 nm using a blank sample of placebo pellets.

A standard curve was generated by serial dilution of a stock solution of the drug in water. Triplicate samples were used for the analysis, and absorbance was measured. The average absorbance of the triplicates obtained from chromatograms was plotted against each STD concentration to generate the calibration curves. the absorbance of three samples was obtained and the average was calculated

ii) Orphenadrine citrate linearity

The linearity that covers the studied concentration range was confirmed using the R^2 of the regression line of the calibration curve.

Also, with pseudoephedrine hydrochloride, the same method was used, but with ʎmax = 214 as described in the USP dissolution protocol.

3.5. Formulation development

As part of the formulation development process, several experimental formulations were produced. These formulations were assessed to see if they met the shape analysis acceptability criteria. After that, quick disintegration was used to evaluate the successful formulation (SF). For SF, characterization of pellets by particle size distribution, size and shape analysis, moisture content, friability, and camera capture of the pellet disintegration process were carried out. To develop drug-loaded formulations, SF was used, and the model drug was added to them. The pellet qualities of these formulations were re-evaluated to confirm that they still had an acceptable shape and fast disintegration. In addition, they were also evaluated for pellet characteristics, as mentioned before. Furthermore, their drug content and dissolution profiles were studied.

3.5.1. General process of preparation

For all experimental formulations, a dry powder mixture of all the ingredients was adjusted within a certain range so that the total weight of all of them would be 65 gm.

The dry powders were loaded into a glass bowl and mixed for 2 minutes with a laboratory-scale blender (Molineux Easy Mix, France) at the lowest speed. Trial and error were used to find the proper amount of binder liquid, which was based on the ability to extrude the mix and the pellet quality. PVP was dissolved in distilled water in a beaker, then PEG400 was added to them. And the solvent was used to moisten the dry mixture. The 5 ml of binder solution was added every 30

seconds while constantly mixing, and the process was continued until the desired plastic mass was obtained. At least twice, the process was paused to scrape down the edges of the bowl and the blade mixer. The resulting wet mass was extruded at 460 RPM speed screw extruder (a modified Molineux HV8 food grinder) through a screen with a 1 mm die diameter and a 3 mm thickness. Around 15 g of fresh extrudates were loaded into the Spheronizer (a modified Molineux coffee grinder) with a cross-hatched friction plate. Spheronization with speeds ranging from 1000 to 5000 rpm was performed on the extrudates until spherical pellets were produced. The resultant pellets were dried by a tray dryer at 50°C for 6 hrs. Finally, a sieve shaker was used to separate the pellets of size fraction 600-850 µm. (Retsch, Germany). After that, the pellets were kept in sealed containers.

To prepare formulations loaded with model drugs, start by directly weighing the exact amount of model drug in a plastic dish and adding it to the dry powder mix mentioned above.

3.5.2. Development of pellets without disintegrant

Various pellet formulations were prepared as described in (Table 7):

Pelletization aid, filler, pore former, binder and water.

Table 7: Composition of the pellet formulations without disintegrant

	MCC (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Water
X1	70.6	14.4	14.4	0.6	Q.s
X2	60	25	14.4	0.6	Q.s
X3	51	34	14.4	0.6	Q.s
X4	65	14.4	20	0.6	Q.s

MCC: Microcrystalline cellulose, PEG: Polyethylene glycol, PVP: Povidone, %: W/w percentage

3.5.3. Development of pellets with disintegrant

To enhance the disintegration time, disintegrants were added to the dry mix (Table 8).

Table 8: Composition of the pellet formulations with disintegrant

	MCC (%)	PPXL (%)	CCS (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Water
P1	47	4		34	14.4	0.6	Q.s
P2	43	8		34	14.4	0.6	Q.s
P3	33.33	16.67		35	14.4	0.6	Q.s
P4	25	25		35	14.4	0.6	Q.s
P5	16.67	33.33		35	14.4	0.6	Q.s
C1	45		5	35	14.4	0.6	Q.s
C2	40		10	35	14.4	0.6	Q.s
C3	35		15	35	14.4	0.6	Q.s
C4	25		25	35	14.4	0.6	Q.s

MCC: Microcrystalline cellulose, PPXL: Polyplasdone XL10, CCS: Croscarmellose sodium, PEG: Polyethylene glycol, PVP: Povidone, %: W/w percentage.

3.5.4. Development of pellets with disintegrant and ethanol.

Ethanol was added to the granulating liquid to modify the disintegration test. (Table 9)

Table 9: Composition of the pellet formulations with disintegrant and ethanol

	MCC (%)	PPXL (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Ethanol (%)	Water
PE1	43	8	34	14.4	0.6	50% v/v water	Q.s

MCC: Microcrystalline cellulose, PPXL: Polyplasdone XL10, PEG: Polyethylene glycol, PVP: Povidone, %: W/w percentage.

3.5.5. Development of pellets with a combination of disintegrants

Combinations of disintegrants were added to the dry mix in an attempt to exploit the potential synergistic behavior of disintegrants with diverse principles of action, such as swelling and water wicking [71]. (Table 10)

Table 10: Composition of the pellet formulations with a combination of disintegrants

	MCC (%)	PPXL (%)	CCS (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Water
CP1	45	2.5	2.5	35	14.4	0.6	Q.s
CP2	40	5	5	35	14.4	0.6	Q.s
CP3	35	5	10	35	14.4	0.6	Q.s
CP4	30	5	15	35	14.4	0.6	Q.s
CP5	30	10	10	35	14.4	0.6	Q.s
CP6	50	5	5	25	14.4	0.6	Q.s
CP7	45	5	10	25	14.4	0.6	Q.s
CP8	40	10	10	25	14.4	0.6	Q.s
CP9	40	15	15	15	14.4	0.6	Q.s
CP10	45	15	15	10	14.4	0.6	Q.s
CP11	40	15	15	9.4	20	0.6	Q.s
CP12	50	5	15	9.4	20	0.6	Q.s

MCC: Microcrystalline cellulose, PPXL: Polyplasdone XL10, CCS: Croscarmellose sodium, PEG: Polyethylene glycol, PVP: Povidone, %: W/w percentage

3.5.6. Development of pellets with a model drug

The developed formula will be uploaded by 5%, 15%, 25%, and 30% separately by two model drugs with different degrees of solubility. Pseudoephedrine hydrochloride, which is freely soluble in water, and orphenadrine citrate, which is sparingly soluble in water.

- Development of pellets with pseudoephedrine hydrochloride (Table 11)

Table 11: Composition of the pellet formulations with pseudoephedrine hydrochloride

	MCC (%)	PPXL (%)	CCS (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Ps. HCl %	Water
CPP1	50	5	15	9.4	20	0.6	+5%	Q.s
CPP2	50	5	15	9.4	20	0.6	+15%	Q.s
CPP3	50	5	15	9.4	20	0.6	+25%	Q.s
CPP4	50	5	15	9.4	20	0.6	+30%	Q.s

MCC: Microcrystalline cellulose, PPXL: Polyplasdone XL10, CCS: Croscarmellose sodium, PEG: Polyethylene glycol, PVP: Povidone, Ps. HCl: Pseudoephedrine hydrochloride, %: W/w percentage

- Development of pellets with orphenadrine citrate (Table 12)

Table 12: Composition of the pellet formulations with orphenadrine citrate

	MCC (%)	PPXL (%)	CCS (%)	Mannitol (%)	PEG 400 (%)	PVP (%)	Orph. Citr. %	Water
CPO1	50	5	15	9.4	20	0.6	+5%	Q.s
CPO2	50	5	15	9.4	20	0.6	+15%	Q.s
CPO3	50	5	15	9.4	20	0.6	+25%	Q.s
CPO4	50	5	15	9.4	20	0.6	+30%	Q.s

MCC: Microcrystalline cellulose, PPXL: Polyplasdone XL10, CCS: Croscarmellose sodium, PEG: Polyethylene glycol, PVP: Povidone, orph, citr.: Orphenadrine citrate, %: W/w percentage

3.6. Characterization of pellets.

Pellets without disintegrant, with PPXL, with CCS, and with a combination of disintegrants were assessed to meet the following acceptance criteria: (Table 13).

Table 13: Acceptance criteria for selection of pellets stage 1 and 2

Stage	Acceptance criteria
Stage 1 **Pellets shape by visual and microscopic examination**	Uniform spherical shape [11]
Stage 2 **Disintegration time**	Disintegrate within the specified period (2.5 to 10 min) [72]

Stage 1 (pellet shape): under the microscope, pellets were observed for their spherical shape and by visual examination.

Stage 2 Disintegration Time (DT): modified USP tablet disintegration apparatus was used to study pellet disintegration. A 300 µm mesh was placed at the bottom of each tube in the basket-rack assembly to prevent pellets from getting out. 100 mg of pellets were placed in each of the 6 tubes of the basket rack assembly, using water at 37± 2°C as the immersion fluid and reducing the volume of fluid in the beaker from 800 ml to 700 ml to ensure that pellets remained in the tube.

The time at which the pellets passed through the 300 µm mesh was recorded as the disintegration time.

3.6.1. The successful formulation

Based on the results of the tests in stages 1 and 2. The SF was chosen. This formulation was assessed by stage 3: particle size distribution, size and shape analysis, moisture content, friability, and camera capture of the pellet disintegration process. (Table 14).

Table 14: Acceptance criteria for selection of pellets stage 3 [11]

Stage 3 analysis	Acceptance criteria
particle size distribution	Narrow, uniform size
Size and shape analysis by image j®	Uniform spherical shape
Moisture content	low
Friability	low

i) Particle size distribution

The pellet particle size distribution was determined by sieve shaking. By arranging a group of standard sieves with different aperture sizes in descending order (1.18 mm, 850, 600, 425, 250 µm) using a sieve shaker (Retsch AS200, Germany) for 5 minutes, the weight portion kept on each sieve was weighed by an analytical balance (ae Adam, USA). Each fraction percentage was calculated. Further investigation was conducted using a fraction size range of 600-850 µm.

ii) Size and shape analysis

Pellet size and shape were evaluated by a USB digital microscope (China) connected to a computer by taking photos of pellets. The license-free image analysis software Image J® was used to analyze the photos. The magnification was set so that one pixel equaled 0.0866 µm, and roughly 100 pellets from the 600-850 µm size fraction of each batch were examined to determine the projected area, perimeter, Feret diameter (mean of 180 caliper measurements with a 1° rotation angle), circularity,

aspect ratio (AR) (the ratio of the longest Feret diameter to its longest perpendicular diameter), roundness, solidity, and sphericity for each pellet.

iii) Pellets yield

Pellets yield which is expressed as the fraction of pellets in the specified size range 600-850 µm.

iv) Moisture content

The pellets were crushed with a mortar and pestle, and the loss on drying (LOD) was determined by heating approximately 5 g precisely weighed samples on a sample pan using a moisture analyzer (OHAUS, Switzerland).

v) Friability

A sample of 11.6 gm of pellets was weighed and put in a friability tester drum with 200 glass beads that have a 4 mm diameter, and the device was rotated at 100 rpm for 4 min. After that, pellets were sieved for 5 minutes through 250 µm mesh to remove fines, and the weight was noted. Friability was then calculated as follows:

$$friabilty = \frac{W1 - W2}{W1} * 100\%$$

w1 is the initial weight of pellets and w2 is the final weight of pellets.

vi) Camera capture of the pellet disintegration process

In addition to the disintegration endpoint studied by the USP tablet disintegration apparatus, when evaluated at a static position, the pellets disintegrate into particles of various sizes. When a few drops of water are applied to the pellets on an opaque surface. A (USB digital microscope, China) connected to a computer was used to capture the disintegration process. The images were captured from the beginning till the pellet disintegrated or exploded into small fragments. Pellet images

were taken every 30 seconds for formulations containing a combination of polyplasdone XL-10® and croscarmellose sodium.

3.6.2. Drug-loaded pellets

SF was used to load model drugs. These formulations were assessed by stage 1, 2, and 3 tests to assure that the pellets produced to meet the acceptance criteria. Assay and dissolution studies were done on these formulations for each API used.

1. Drug content

1.1. Pseudoephedrine hydrochloride

2220.33 mg of pellets were dissolved in 1-L VF by 1 molar sodium hydroxide with the help of sonication. The volume was completed by purified water, then diluted by 5 ml in 200 ml volumetric flasks filtered through a 0.45 m membrane filter, and the absorbance was measured by UV. In addition, a calibration curve was used to calculate the drug content of pseudoephedrine hydrochloride.

1.2. Orphenadrine citrate

294.75 mg pellets were dissolved in 250 ml VF by one molar sodium hydroxide with the help of sonication, and the volume was completed by purified water, then diluted by 2 ml in 20 ml volumetric flasks filtered through a 0.45 m membrane filter, and the absorbance was measured by UV. In addition, a calibration curve was used to calculate the drug content of orphenadrine citrate.

2. Dissolution test

2.1. Pseudoephedrine hydrochloride

To evaluate the effects of the factors under investigation on drug release. The in vitro release profile was studied using the USP dissolution apparatus II with the rotational speed of 50 rpm, the temperature of 37°C, and 900 ml dissolution medium. The six chambers were filled with 100 mg of pellets (equivalent to 30 mg of pseudoephedrine hydrochloride). At 5, 10, 20, 30, 45, and 60 minutes, 5ml samples were taken from the dissolution apparatus and filtered through a 0.45 m membrane filter, then analyzed as USP condition (Table 15) by UV to measure the pseudoephedrine hydrochloride absorbance at each time point.

The concentration of pseudoephedrine hydrochloride was calculated by taking the linearity equation from the calibration curve, multiplying it by the chamber volume, and then dividing it by the actual amount of pseudoephedrine hydrochloride in pellets.

Table 15: Pseudoephedrine hydrochloride dissolution test specifications [73]

Properties	Specification
Medium	900 ml water
Speed	50 rpm
Time	5, 10, 20, 30, 45, 60
Instrumental condition mode	UV 214 nm

2.2. Orphenadrine citrate.

Also, for orphenadrine citrate, the in vitro release profile was investigated using the dissolution apparatus II. The six chambers were filled with 100 mg of pellets (equivalent to 30 mg of orphenadrine citrate). At 5, 10, 20, 30, 45, and 60 minutes, samples were taken from the dissolution apparatus and analyzed as USP conditions (Table 16) by UV to measure the orphenadrine citrate absorbance at each time point.

The orphenadrine citrate concentration was calculated by using the linearity equation derived from the calibration curve, multiplied by the dilution factor, then multiplied by chamber volume, and finally divided by the orphenadrine citrate actual quantity in pellets.

Table 16: Orphenadrine citrate dissolution test specifications [74]

Properties	Specification
Medium	900 ml water
Speed	50 rpm
Time	5, 10, 20, 30, 45, 60
Instrumental condition mode	UV 210 nm

Chapter IV: Results and discussion

4. Results and discussion

4.1. UV analysis results

4.1.1. Calibration curve and linearity

4.1.1.1. Orphenadrine citrate

The results of linearity study of orphenadrine citrate concentration are shown in (Table 17). For each concentration, the absorbance of three samples was obtained and the average was calculated.

Table 17: Concentration of orphenadrine citrate and absorbance of each.

STD#	conc. (mg/ml)	absorbance			Avg. abs.	SD	RSD
		1	2	3			
STD1	0.003	0.136	0.134	0.136	0.135	0.001	0.85
STD2	0.005	0.221	0.219	0.220	0.220	0.001	0.45
STD3	0.008	0.358	0.360	0.357	0.358	0.002	0.43
STD4	0.01	0.439	0.443	0.441	0.441	0.002	0.45
STD5	0.015	0.652	0.655	0.652	0.653	0.002	0.27
STD6	0.02	0.874	0.876	0.874	0.875	0.001	0.13

Conc.: concentration, avg. abs.: average absorbance, SD: standard deviation, RSD: relative standard deviation

By plotting the concentration of standards versus average absorbance. (Figure 19) shows the regression line equation (y = 43.388x + 0.0059) of orphenadrine citrate, with an R^2 value of 0.9999.

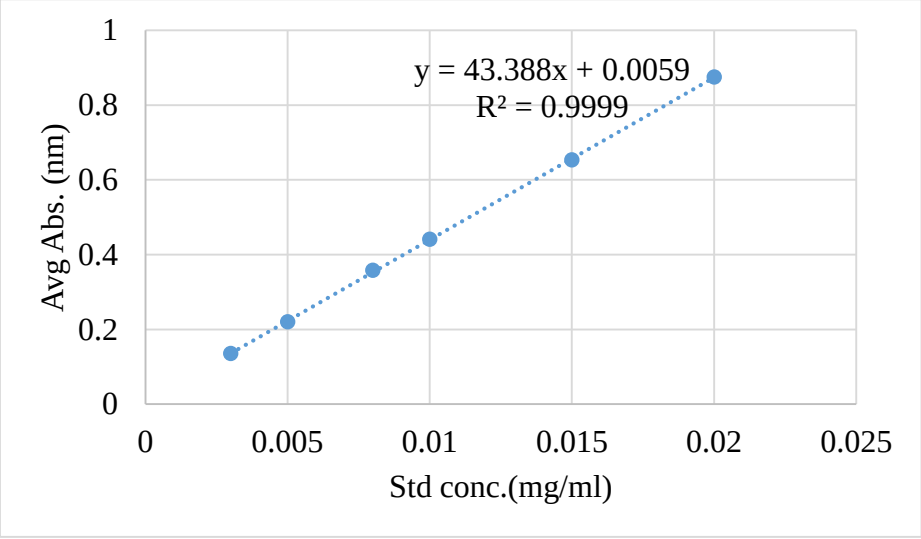


Figure 19: Calibration curve for orphenadrine citrate

4.1.1.2. Pseudoephedrine hydrochloride

The results of the linearity study of pseudoephedrine hydrochloride concentration are shown in (Table 18). For each concentration, the absorbance of three samples was obtained, and the average was calculated.

Table 18: Concentration of pseudoephedrine hydrochloride and absorbance of each

STD#	conc. (mg/ml)	absorbance			Avg. abs.	SD	RSD
		1	2	3			
STD1	0.005	0.133	0.135	0.137	0.135	0.002	1.48
STD2	0.008	0.203	0.201	0.203	0.202	0.001	0.57
STD3	0.01	0.250	0.250	0.254	0.251	0.002	0.92
STD4	0.015	0.377	0.373	0.376	0.375	0.002	0.55
STD5	0.02	0.495	0.496	0.497	0.496	0.001	0.20
STD6	0.03	0.733	0.731	0.731	0.732	0.001	0.16
STD7	0.04	0.976	0.969	0.969	0.971	0.004	0.42

Conc.: concentration, avg. abs.: Average absorbance, SD: Standard deviation, RSD: Relative standard deviation

By plotting the concentration of standards versus average absorbance. (Figure 20) shows the regression line equation ($y = 23.959x + 0.0137$) of pseudoephedrine hydrochloride, with an R^2 value of 0.9999.

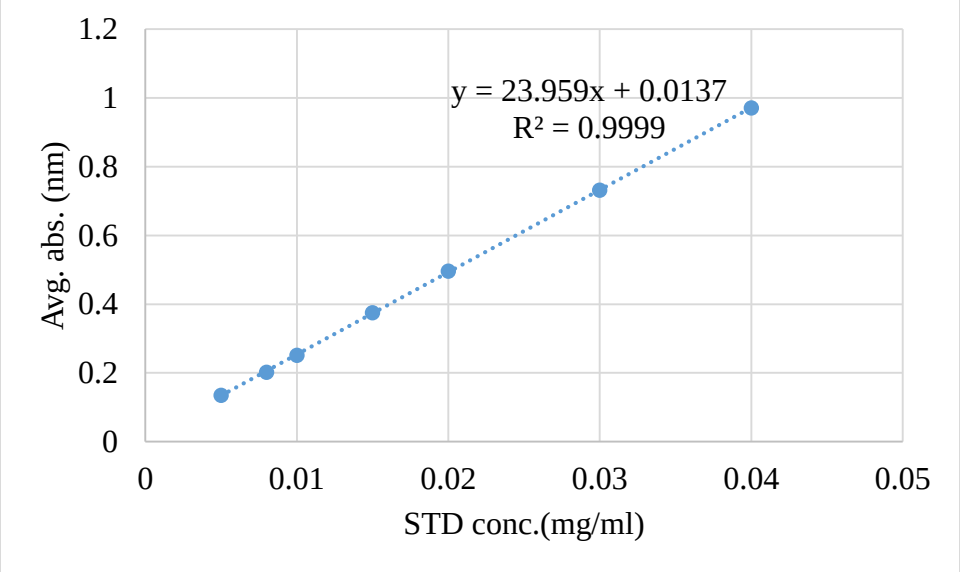


Figure 20: Calibration curve for pseudoephedrine hydrochloride

Over the ranges of (0.005-0.04) mg/ml for pseudoephedrine hydrochloride and (0.003-0.02) mg/ml for orphenadrine citrate, the R^2 values showed a linear relationship between concentrations and absorbance.

4.2. Formulation development

Many operational variables can influence pellet characteristics during the extrusion, spheronization, and drying stages. Extruder speed, extruder screen thickness, and hole diameter, friction plate type, spheronization time, speed, and load, drying temperature, and time are all variables that determine the final pellet quality. In the current research, the different process parameters utilized for pellet preparation are spheronization load, speed, and time [34].

Final pellet quality would also be affected by formulation variables such as the addition of binder, filler, disintegrant, pore former, and type and quantity of granulating liquid. The success of the method can be described as formulation-dependent [34].

For formulation development, it was revealed that MCC, as a spheronizing aid, has a significant impact on sphericity when combined with a granulating solvent, such as water, which functions as a plasticizer. Furthermore, MCC slows pellet disintegration and affects disintegration time and, as a result, pellet dissolution [3].

Hence, a large number of experiments were conducted to properly study the influence of formulation and process parameters on pellet quality and the selection of suitable excipients to achieve the goal of the study.

4.2.1. Development of pellets without disintegrant

Optimization of Process Parameters

The formulation development process started with the preparation and evaluation of the pellet formulation without disintegrants.

The impact of formulation and process variables on pellet roundness and size distribution was investigated, and secondly, the appropriate limits of variables were defined.

To evaluate the possibility of pellet formation, several formulations (X1 to X4) (Table 7) were prepared using MCC PH 101 as a palletization aid. Initial studies were undertaken with various percentages of soluble filler mannitol added to MCC, granulated with different amounts of binder solution of PVP and water and PEG 400 until achieving a soft wet mass. The PVP range was determined based on early trials with the formation of a minimum proportion of fines during spheronization. Then the resulting wet mass was extruded at a constant speed by a screw extruder and the extrudates were spheronized and dried.

To investigate the effects of mannitol and PEG 400 on the properties of MCC PH 101 pellets, the percentages of different excipients used in formulations X1 to X4 were correlated with spheronization load, speed, and time as variables in an experiment.

The results of (X1-X4) samples (Table 19), revealed that the superior water amount was 1:1 of the MCC weight. A clear linear relationship between water content and MCC fraction was found. The amount of water required for successful extrusion increased as the percentage of MCC in the formulation increased. Utilizing a small amount of water in the wet massing stage led to the production of less cohesive, brittle extrudates that are more prone to being destroyed by the rotating plate resulting in either higher production of fines or the formation of an extrudate that, despite its

length reduction, remains cylindrical or “dumbbell” shaped. Also, when a large amount of water was used, sticky dough was produced, resulting in the formation of significantly large pellets under centrifugal force [26].

- **Optimization of spheronization load**

To identify the most suitable load, the extrudate produced in each batch from formulation X1 to X4 was separated into three samples of roughly 10 gm, 15 gm, and 20 gm. Each sample was spheronized at a fixed speed and time (3000 RPM for 30 seconds). The plate must be loaded properly in order for the extrudate to be “chopped” and the fragments to travel in a toroidal motion. The results showed that the appropriate weight for the spheronizer was 15 grams to produce more spherical pellets. When using the plate load at 10 gm, particle-particle interaction was insufficient, and tiny irregular pellets were produced. When using 20 gm, the particles were unable to freely contact the spheronizer plate, resulting in a long time to produce spherical particles [26].

- **Optimization of spheronization speed**

To investigate the impact of spheronization speed on the final shape of pellets, the extrudate produced was divided into three samples of approximately 15 gm that were spheronized at different speeds and fixed times of 30 seconds. The device offers a range of spheronization speeds: (1000-5000 RPM).

The findings showed that the best spheronization speed was to start with a 3000 RPM speed to cut off the extrudate at a shorter length and then lower the speed to 1000 RPM to reduce fine production and allow for spherical pellet formation. At low speed, the greatest variability in shape and size characteristics were observed. The extrudate could break down into small particles at this speed, but due to the low energy input, the cyclinders' plastic deformation was not always complete, as particle/particle and particle/spheronizer interactions were insufficient and bone-

shaped particles were produced, while at high speed, the extrudate was broken up and a high percentage of fines were produced [30].

- **Optimization of spheronization time**

The extrudate produced in each batch was divided into five samples of approximately 15 gm each, which were spheronized at 3000 RPM speeds, then 1000 RPM speeds, for 10, 30, 60, 90, and 120 seconds, respectively.

According to the findings, a short spheronization time (around 30 seconds) was enough to create pellets with the highest yield and adequate sphericity. Lower spheronization time (10 seconds) led to the production of irregular and rough pellets, because the particles did not have enough time to round off, and therefore "bone" shaped particles were produced. Longer spheronization periods (> 120 seconds) did not increase pellet sphericity, but they did promote pellet agglomeration and widening of the pellet size distribution [30].

As per the previous results, the most spherical pellets were achieved at a 15 gm spheronization load and with a spheronization speed of 3000 RPM speed, then 1000 RPM speed, and 30 seconds time.

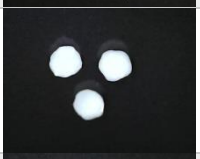
Referring to the above studies pellets were produced at the optimum process parameters and pellets sphericity and size distribution were evaluated visually and by microscopic examination. The results of pellets evaluation are showed in (Table 19).

All formulations (X1 to X4) showed a good spherical shape, as evidenced by a pellet roundness of > 0.92, which is close to 1 as shown in (Table 19). A high percentage of MCC gave robustness to the formula and allowed different time intervals for spheronization without affecting the final pellet shape.

However, a high MCC percentage retarded pellet disintegration time due to the high shrinkage of its structure during drying, which prevented water entry into the pellets [11] [12].

As illustrated in (X1 to X4, Table7) MCC pellets containing mannitol and PEG did not disintegrate after 2 hours, even when the mannitol content was increased to 34% and the PEG 400 was increased to 20%.

Table 19: Stage 1 and 2 results of the pellets formulation without disintegrant

Formula #	S. time	S. load	speed	Microscopic image	Roundness			Pass /fail	DT	Pass/ fail
					Pellet #					
					1	2	3			
X1	90 sec.	15 gm	3000 RPM		0.971	0.942	0.955	Pass	> 2 hrs	Fail
X2	60 sec	15gm	3000 RPM		0.940	0.940	0.920	Pass	> 2 hrs	Fail
X3	90 sec	15 gm	3000 RPM		0.963	0.964	0.950	Pass	> 2 hrs	Fail
X4	120 sec	15 gm	3000 RPM		0.928	0.931	0.920	Pass	> 2 hrs	Fail

S. time: Spheronization time, S. load: Spheronization load, DT: Disintegration time, min.: Minute

4.2.2. Development of pellets with disintegrant

In order to enhance pellets disintegration, super-disintegrants were added and an adequate amount of MCC was utilized to maintain sphericity to pellets. Several formulations (P1 to P5 and C1 to C4, Table 8) were produced utilizing PPXL, CCS to evaluate the effect of super-disintegrant.

Based on the results sphericity was negatively affected by CCS. Pellet sphericity reached a maximum distortion at (15% and 25%) (C3 & C 4) of CCS content. While PPXL has no direct

influence. All the formulations in (Table 20) showed a good spherical shape. As evidenced by a pellet roundness of > 0.82, which is close to 1, except for C3 and C4, which have a clear roughness and distortion of the surface in addition to the wide size distribution.

The results of pellet evaluation (Table 20) for the DT of different formulations showed that formulations P1 and P2 with (4% & 8%) PPXL content have no significant effect on DT. While P3 to P5 (16.67%, 25%, and 33.33%) of PPXL content improves slightly, it disintegrates after more than 30 minutes.

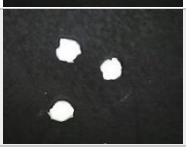
The disintegration time is determined by the CCS level. Lower CCS content formulations C1 to C3 (5%, 10%, and 15%) performed slightly better and disintegrated after 30 minutes. While a higher CCS content of 25%; C4 results in a significant reduction, the pellets explode and disintegrate into smaller pieces within 2 minutes. Possibly, this was expected due to the CCS disintegrant's swelling effect, which forces the pellets to become explode and facilitate water entry [15], but the formula failed the shape test due to the pellet shape distortion. As a result, there is a need to improve pellet shape.

Disintegration time (DT) is often influenced by the binder and disintegrant used. The binder is used at a fixed value, the lower active limit in all formulations (0.5%). DT fluctuated based on the disintegrant concentrations in the formulation, with an inverse relationship with the disintegrant. PPXL has good hydration ability and elevated capillary efficiency by wicking with little swelling effect compared to CCS [3].

The super-disintegrant CCS had an effect on friability and disintegration time. Swelling of CCS was noticed during granulation of the dry blend, which was directly related to the amount of CCS employed in the formulation. Regardless of binder concentration, the higher the proportion of CCS

employed, the more swelling occurred, resulting in the formation of more fines during spheronization. CCS expands as it comes into contact with water, necessitating more water for pelletization[3].

Table 20: Stage 1 and 2 results of the pellets formulation with disintegrant

Formula #	S. time	S. load	speed	Microscopic image	Roundness Pellet #			Pass/ fail	DT	Pass/ fail
					1	2	3			
P1	30 sec.	15 gm	3000 RPM		0.975	0.946	0.939	Pass	> 2 hrs	Fail
P2	30 sec.	15 gm	3000 RPM		0.932	0.828	0.821	Pass	> 2 hrs	Fail
P3	30 sec.	15 gm	3000 RPM		0.910	0.945	0.914	Pass	> 30 min	Fail
P4	30 sec.	15 gm	3000 RPM		0.916	0.918	0.902	Pass	> 30 min.	Fail
P5	30 sec.	15 gm	3000 RPM		0.942	0.883	0.911	Pass	> 30 min.	Fail
C1	30 sec.	15 gm	3000 RPM		0.909	0.849	0.996	Pass	> 30 min.	Fail
C2	30 sec.	15 gm	3000 RPM		0.838	0.968	0.942	Pass.	> 30 min.	Fail
C3	30 sec.	15 gm	3000 RPM		0.946	0.893	0.888	Fail	> 30 min.	Fail
C4	30 sec.	15 gm	3000 RPM		0.923	0.938	0.810	Fail	< 2 min.	Pass

S. time: Spheronization time, S. load: Spheronization load, DT: Disintegration time, min.: Minute

4.2.3. Development of pellets with disintegrant and ethanol.

In a trial to enhance P1 formulation, which has better shape roundness > 0.939, because PPXL alone was insufficient to meet DT's needs, PE1 was prepared using 99% ethanol 50/50 v/v of water to granulate the dry mixture, but the wet mass became like chewing gum and did not extrude. And no pellets were produced.

4.2.4. Development of pellets with a combination of disintegrants

Another attempt was made to get fast disintegrating pellets with a desirable shape by taking advantage of the potential synergistic behavior of disintegrants with diverse principles of action, such as swelling and water wicking [71].

Several pellet formulations were prepared using a combination of CCS and PPXL as described in (CP1 to CP12, Table 10). Based on the results sphericity was negatively affected by the combination of PPXL and CCS. CP1 to CP11 formulation (Table 21) showed no shape enhancement. As evidenced by a pellet image, which has a clear roughness and distortion of the surface in addition to a high percentage of fine. Only CP12 achieved the required spherical and smooth surface pellets.

The results of pellet evaluation (Table 21) for the DT of different formulations showed that while the CP1 formulation improves slightly, it disintegrates after more than 30 minutes.

Second formulations CP2, CP3, and CP4, were prepared by increasing the CCS concentration with a fixed concentration of PPXL. CP2 and CP3 improved slightly, but they disintegrated after more than 30 minutes. While CP4 achieved a desirable DT (less than 2 min), it was noticeable that using 15% of CCS had a positive effect on DT.

One more formulation, CP5, was prepared by increasing PPXL with a fixed CCS content. No significant change in DT was seen.

Other formulations CP6, CP7, and CP8 were prepared by increasing MCC content and lowering mannitol content while keeping PPXL and CCS concentrations constant in CP2, CP3, and CP5, respectively. There were no notable changes in DT.

Another formulation, CP9, and CP10, were made with an equal amount (15%) of PPXL and CCS, and faster DT were observed (less than 30 min.)

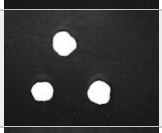
The last formulations, CP11, and CP12, were made by increasing PEG content to (20%) and using a fixed percentage of CCS (15%), 15%, and 5% PPXL, respectively, and the results show a clear improvement in DT (less than 2 min.).

Also, we noticed in CP9–CP11 that the extrudes were fragile, so a low-speed spheronizer 1000 RPM was used.

Also, we observed that increasing the PEG 400 concentration to 20% w/w resulted in smaller, more spherical, and smoother pellets. This result is supported by a study that indicated combining hydrophilic polymers with Avicel's lower wet mass consistency allows for easier extrusion, resulting in spherical, smoother pellet surfaces and smaller pellet sizes [4]

The composition of pellets had a significant effect on the disintegration time of all formulations. Both the hydrophilicity of PEG and the solubility of mannitol had a limited ability to disintegrate the matrix of pellets, but when combined with CCS and PPXL, they increased pellet disintegration by swelling and wetting of the pellet core. The combination of these approaches has a synergistic effect on pellet formation, overcoming the problem of drug disintegration in extruded MCC pellets [71].

Table 21: Stage 1 and 2 results of the pellets formulation with a combination of disintegrants

Formula #	S. time	S. load	speed	Microscopic image	Roundness			Pass/ fail	DT	Pass/ fail
					Pellet #					
					1	2	3			
CP1	30 sec.	15 gm	3000 RPM		0.956	0.706	0.977	Fail	> 30 min.	Fail
CP2	30 sec	15gm	3000 RPM		0.872	0.897	0.854	Fail	> 30 min.	Fail
CP3	30 sec	15gm	3000 RPM		0.857	0.883	0.926	Fail	> 30 min.	Fail
CP4	30 sec	15gm	3000 RPM		0.829	0.887	0.823	Fail	< 2 min.	Pass
CP5	30 sec	15gm	3000 RPM		0.889	0.850	0.872	Fail	> 30 min.	Fail
CP6	30 sec	15gm	3000 RPM		0.859	0.990	0.952	Fail	> 30 min.	Fail
CP7	30 sec	15gm	3000 RPM		0.915	0.966	0.888	Fail	> 30 min.	Fail
CP8	30 sec	15gm	3000 RPM		0.952	0.867	0.882	Fail	> 30 min.	Fail
CP9	60 sec.	15gm	1000 RPM		0.816	0.924	0.940	Fail	< 30 min.	Pass
CP10	30 sec.	15gm	1000 RPM		0.894	0.926	0.932	Fail	< 30 min.	Pass
CP11	30 sec.	15gm	1000 RPM		0.880	0.871	0.756	Fail	< 2 min.	Pass
CP12	30 sec.	15gm	3000 RPM		0.947	0.915	0.949	Pass	< 2 min.	Pass

s. time: Spheronization time, S. load: Spheronization load, DT: Disintegration time, min.: Minute

CP12 was considered a successful formula, and pellet characterization results were as follows:

4.2.5. Successful trial formulation evaluation

I. Particle size distribution

The results of the particle size distribution for formula CP12 are shown in (Table 22). The test was performed by a sieve shaker. The results revealed that the majority (82.67%) of the CP12 batch pellets ranged from 600 to 850 µm. As a consequence, this size fraction was chosen for further study. Pellets usually come in size range of (0.5-2) mm [6]. This shows that our outcomes are satisfactory.

Table 22: Results of CP12 pellets size distribution by sieve analysis

Mesh size number	Sieve #	mesh size (µm)	weight retained on each sieve (g)	Percent retained on each sieve (%)	Cumulative percent retained on each sieve (%)	Percentage passing (%)
16	6	1180	0.03	0.26	0.26	99.74
20	5	850	0.04	0.34	0.60	99.40
30	4	600	9.59	82.67	83.28	16.72
40	3	425	1.21	10.43	93.71	6.29
60	2	250	0.49	4.22	97.93	2.07
Pan	1	------	0.24	2.07	100.00	00

µm: Micrometer, g: Gram.

% retained = (Weight of pellets retained over x # sieve/Actual weight of pellets) *100

Pellets weight = 11.6 gm.

As shown in (Figure 21) 10% of the sample is smaller than 444.9 µm, 50% is smaller than 529.56 µm, and 90% is smaller than 761.07 µm.

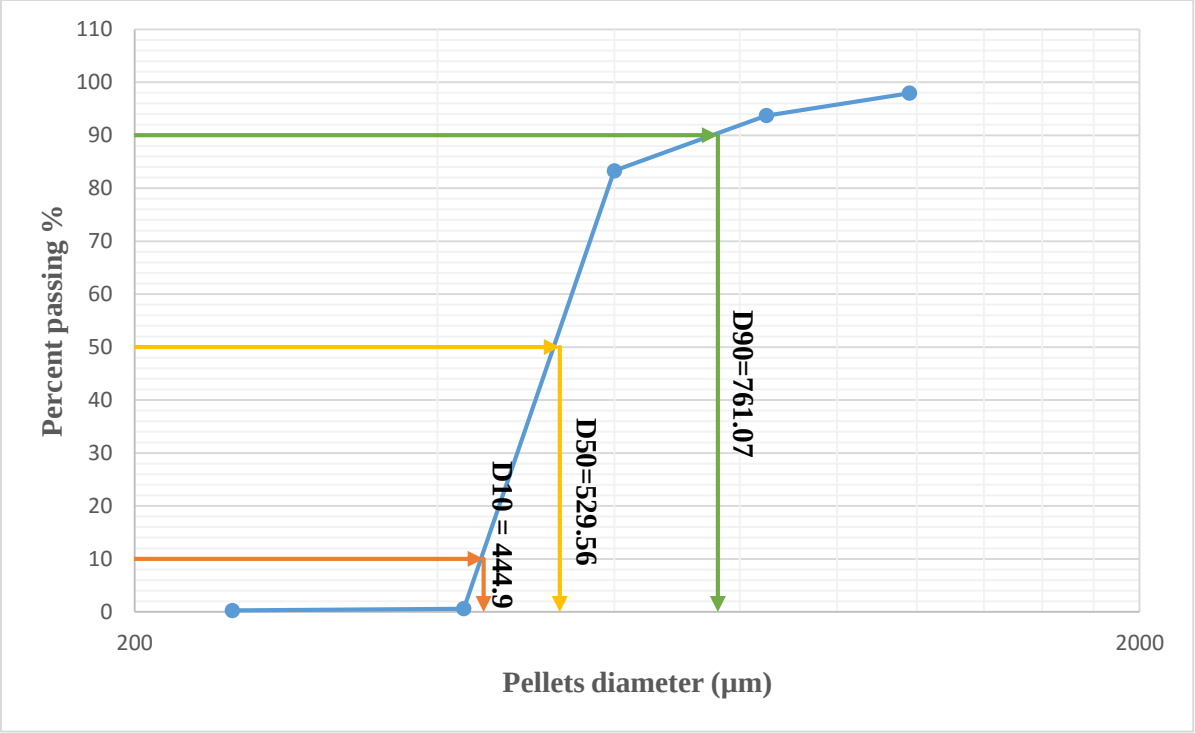


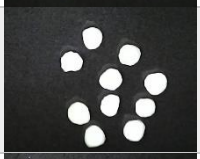
Figure 21: Particle size distribution by sieving for formula CP12

II. Size and shape analysis

The results of size and shape analysis are shown in (Table 23). The test was performed by image J ® free software. The pellets in the majority of the CP12 batch were approximately spherical with a roundness range between (0.88-.93).

All CP12 pellets have an aspect ratio in the range of (1.08–1.14), which is within the limit (an aspect ratio of 1.00 denotes an ideal spherical shape; in practice, values up to 1.2 are allowed) [15].

Table 23: Results of size and shape analysis for formula CP12

Pellet group #	Average Area = $A\pi r^2$ (µm2)	A/ π	R = SQRT (A/ π)	D (µm) = R*2	P.	F. D. (µm)	C.	AR	RN.	Microscopic image
1	510857	162611	403	807	2687	871	0.89	1.10	0.91	
2	394223	125485	354	708	2362	771	0.89	1.12	0.90	
3	434759	138388	372	744	2498	816	0.87	1.14	0.88	
4	480388	152912	391	782	2669	855	0.85	1.13	0.89	
5	454227	144585	380	760	2542	830	0.88	1.11	0.90	
6	459254	146185	382	765	2547	819	0.89	1.08	0.93	
7	486055	154716	393	787	2620	852	0.89	1.12	0.90	
8	496802	158137	398	795	2669	868	0.87	1.09	0.92	
9	443173	141066	376	751	2527	819	0.87	1.11	0.90	
10	476108	151550	389	779	2620	846	0.87	1.10	0.91	

A: Area., SQRT: Square root, D: Diameter, R: Radius F. D.: Ferret diameter, P: Perimeter, C: Circularity, AR: Aspect ratio, RN.: Roundness

Pellet size distribution for formula CP12 derived from estimated pellet diameter from image J® software is shown in (Figure 22). As it is illustrated that 85% of the sample has a diameter range (717-822 µm) which indicates the sample has a narrow size distribution.

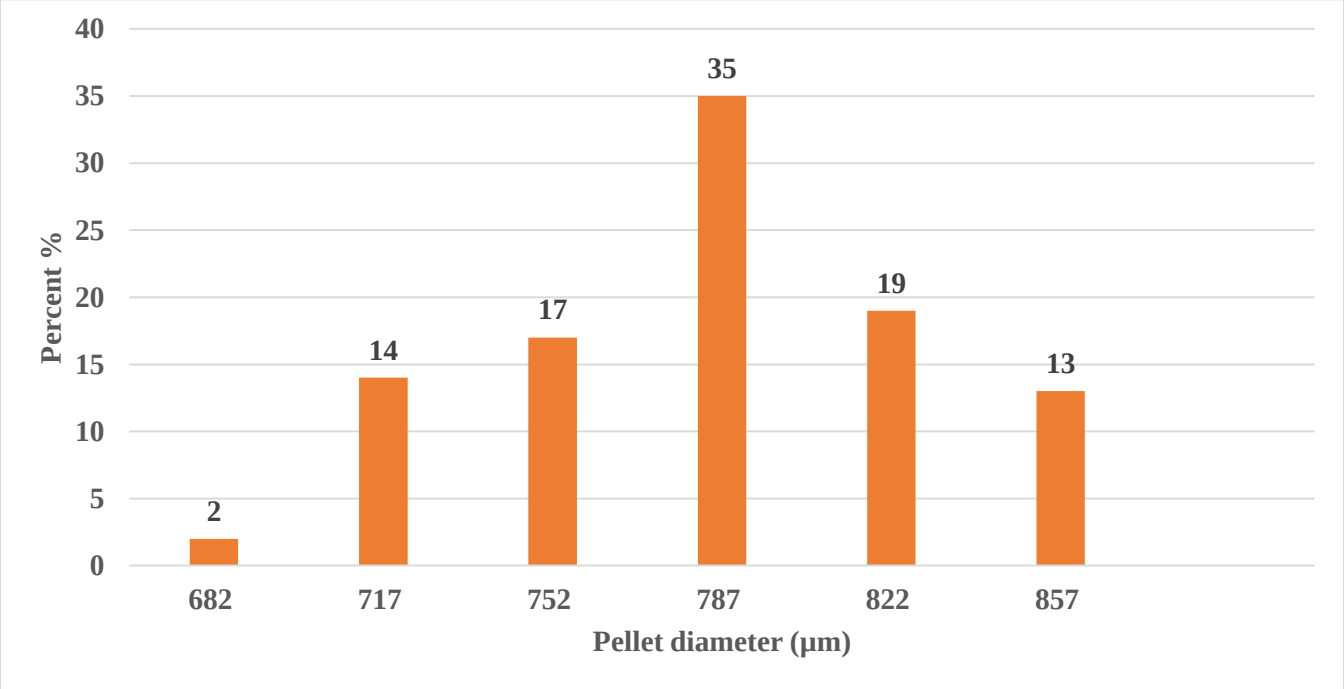


Figure 22: Pellets size distribution by image j® software for formula CP12

III. Pellets yield

Pellets yield by sieve analysis for 600-850 µm were depicted in (Figure 23) and it was excellent (82.67%)

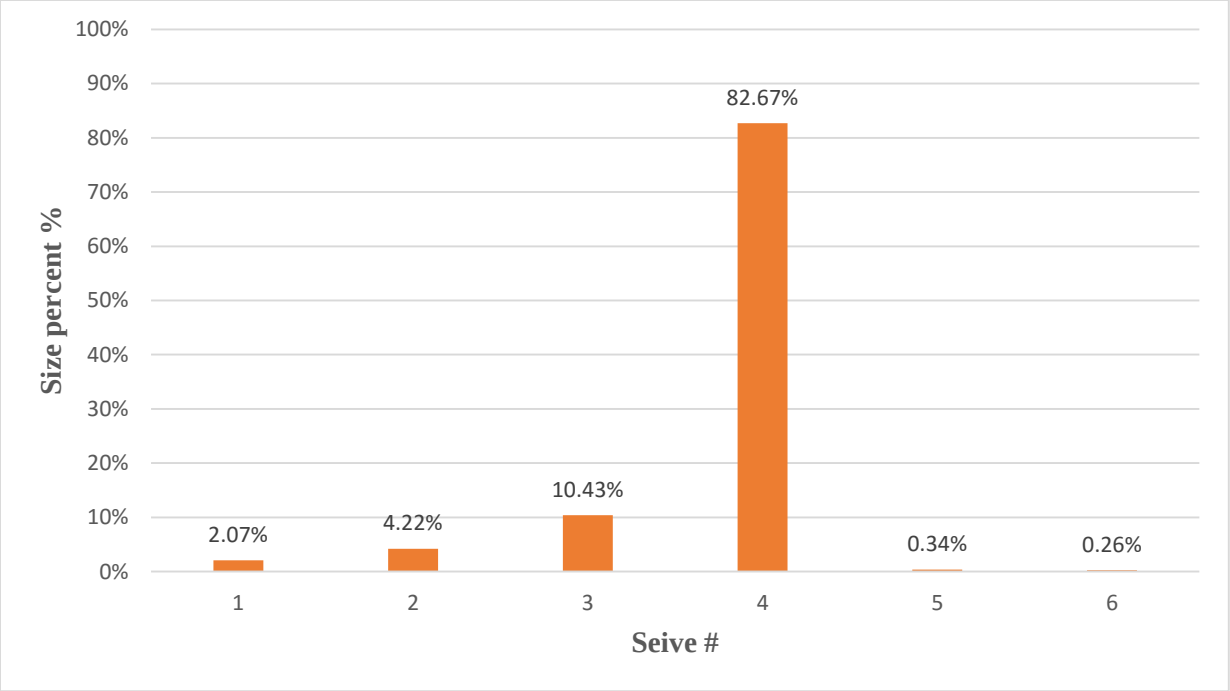


Figure 23: Results of CP12 pellets yield

IV. Moisture content

The scale directly reported the % weight loss due to moisture loss. CP12 pellets L.O.D = 4.6 is an acceptable value, high moisture content deteriorate disintegration.

V. Friability

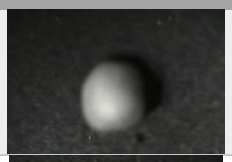
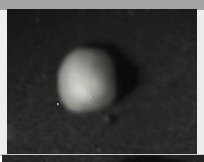
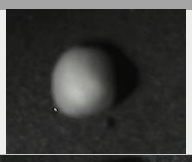
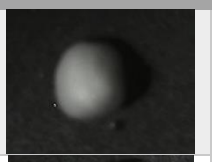
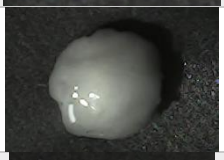
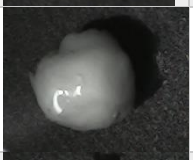
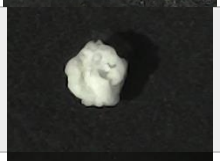
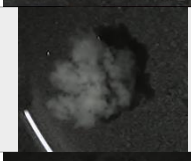
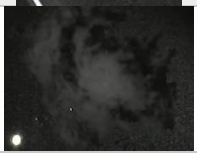
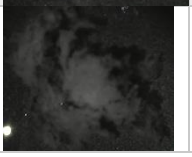
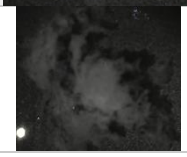
The test was performed by the friabilator. Friability was estimated to be 0.6% that is considered within acceptable limits (less than 1%). See appendix A

VI. Camera capture of the pellet disintegration process

The disintegration process was evaluated at room temperature under a static situation. And the camera captured images every 30 seconds as depicted in (Table 24), properly illustrating that MCC pellets X3 with mannitol and PEG 400 did not disintegrate. Within 120 seconds, cracks appear in

the P5 pellets containing mannitol, PEG, and PPXL. While, as seen in C4 pellets, they begin to explode into many fragments within 30 seconds. Moreover, it is clearly proven that the CP12 pellets that contained PEG 400, mannitol, CCS, and PPXL began to explode into many pieces of loosely linked particles after 60 s, which easily separated under the oscillating motion of the USP disintegration equipment. The photos are compatible with the above-mentioned results from the USP disintegration device. With a temperature increase to 37 °C, the disintegration caused the split into tiny fragments. Although this is not an official USP test, using video capture for disintegration validates Benchawan Chamsai's claims of quick disintegration [15].

Table 24: Camera capture of CP12 pellet disintegration at different time intervals

Pellet #	0 sec.	30 sec.	60 sec.	90 sec.	120 sec.
X3					
P5					
C4					
CP12					

Sec.: Second

4.2.6. Drug-loaded pellets

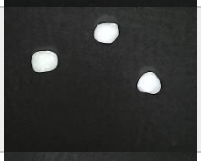
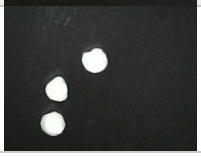
Hence, the optimized concentration of a successful formulation, which grants low DT and an acceptable appearance, was used for uploading model drugs. The solubility of the drugs has a significant effect on the amount of water needed to make suitable pellets and on their physical properties. Drugs that are sparingly water soluble, such as orphenadrine citrate, are mostly

suspended during the extrusion/spheronization process and so require additional water. In contrast, water-soluble drugs such as pseudoephedrine hydrochloride are dissolved to a significantly greater level during extrusion. Consequently, the pelletization process requires less water.

4.2.6.1. Pseudoephedrine hydrochloride

Pseudoephedrine hydrochloride was used as a model drug that is freely soluble in water. The DT of several batches is shown in (Table 11 and 25), as the formulation used offers a desirable shape and fast DT.

Table 25: Stage 1 and 2 results of the pellets formulation with pseudoephedrine hydrochloride

Formula #	S. time	S. load	speed	Microscopic image	Roundness			Pass / fail	DT	Pass / fail
					Pellet #					
					1	2	3			
CPP1	30 sec.	15gm	3000 RPM		0.983	0.980	0.979	Pass	< 5 min.	Pass
CPP2	30 sec.	15gm	3000 RPM		0.903	0.857	0.919	Pass	< 5 min.	Pass
CPP3	30 sec.	15gm	3000 RPM		0.820	0.806	0.911	Pass	< 5 min.	Pass
CPP4	30 sec.	15gm	3000 RPM		0.935	0.908	0.961	Pass	< 5 min.	Pass

S. time: Spheronization time, S. load: Spheronization load, DT: Disintegration time, min.: Minute

I. Particle size distribution

The results of particle size distribution for formula CPP4 are shown in (Table 26). The test was performed by a sieve shaker. The outcomes revealed that the majority (79.14%) of the CPP4 batch pellets ranged from 600 to 850 µm. As a consequence, this size fraction was chosen for further

study. Pellets usually come in the size range of 0.5-2 mm [6]. This shows that our outcomes are satisfactory.

Table 26: Results of pseudoephedrine hydrochloride pellets size distribution by sieve analysis

Mesh size number	Sieve #	mesh size (µm)	weight retained on each sieve (g)	Percent retained on each sieve (%)	Cumulative percent retained on each sieve (%)	Percentage passing (%)
16	6	1180	0.2	1.87	1.87	98.13
20	5	850	1.81	16.93	18.8	81.2
30	4	600	8.46	79.14	97.94	2.06
40	3	425	0.18	1.68	99.62	0.38
60	2	250	0.02	0.19	99.81	0.19
Pan	1	------	0.02	0.19	100.00	00

µm: Micrometer, g: Gram.

% retained = (Weight of pellets retained over x# sieve/Actual weight of pellets) *100

Pellets weight = 10.69 gm

As shown in (Figure 24), 10% of the sample is smaller than 625.08 µm, 50% is smaller than 751.44 µm, and 90% is smaller than 1021.53 µm.

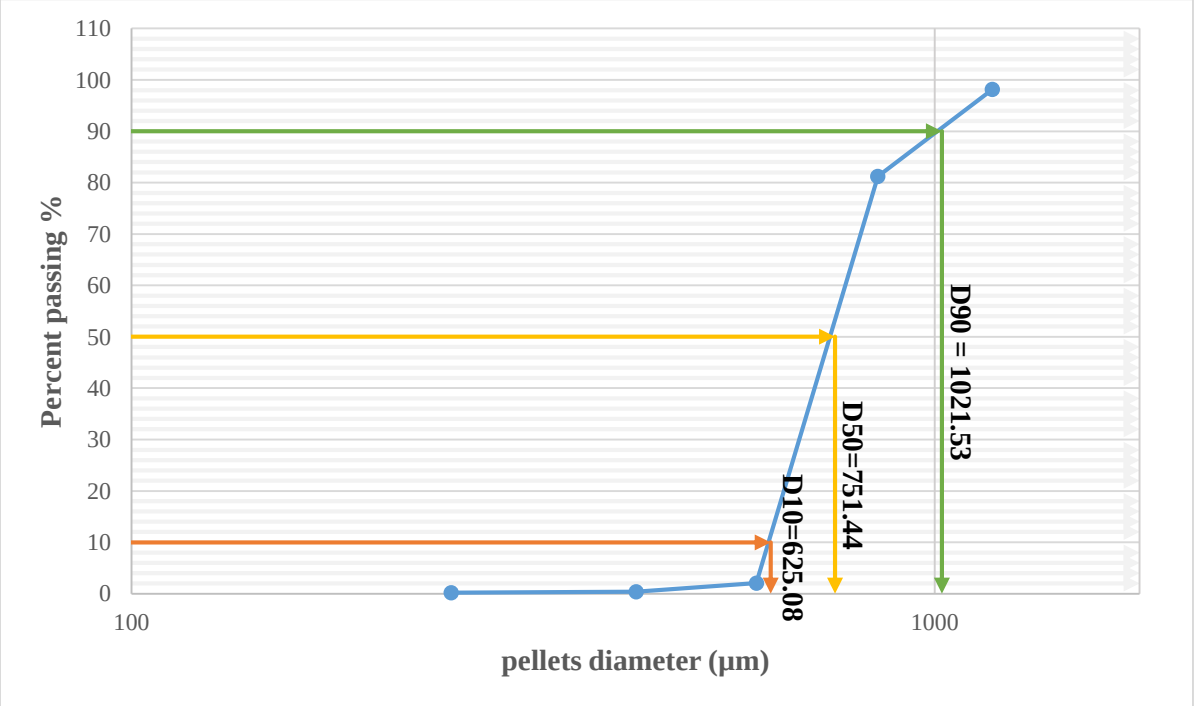


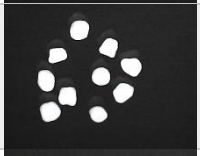
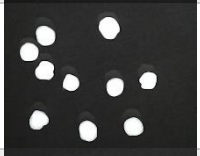
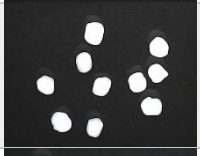
Figure 24: Pseudoephedrine hydrochloride pellets size distribution by sieve analysis

II. Size and shape analysis by image J®

The results of size and shape analysis are shown in (Table 27). The test was performed by image J® free software. The pellets in the majority of the CPP4 batch were approximately spherical with a roundness range of between (0.85-0.91).

All pellet formulations have an aspect ratio in the range of (1.10–1.18), which is within the limit (an aspect ratio of 1.00 denotes an ideal spherical shape; in practice, values up to 1.2 are allowed) [15].

Table 27: Results of pseudoephedrine hydrochloride size and shape analysis

Pellet group #	Average Area = R2 π (µm2)	A/ π	R = SQRT(A/ π)	D (µm) = R*2	P.	F.D. (µm)	C.	AR	RN.	Microscopic image
1	511323	162759	403	807	2742	905	0.85	1.17	0.86	
2	407117	129589	360	720	2421	808	0.87	1.16	0.87	
3	407197	129615	360	720	2427	809	0.87	1.17	0.86	
4	450253	143320	379	757	450253	837	0.88	1.17	0.86	
5	447933	142581	378	755	2528	836	0.88	1.16	0.87	
6	435306	138562	372	744	2492	818	0.88	1.12	0.90	
7	427212	135986	369	738	2477	820	0.87	1.18	0.85	
8	410837	130774	362	723	2403	786	0.89	1.10	0.91	
9	446720	142195	377	754	2535	827	0.87	1.12	0.90	
10	419091	133401	365	730	2442	810	0.88	1.16	0.87	

A: Area., SQRT: Square root, D: Diameter, R: Radius F. D.: Ferret diameter, P: Perimeter, C: Circularity, AR: Aspect ratio, RN.: Roundness.

Pellet size distribution for formula CPP4 derived from estimated pellet diameter from image J® software is shown in (Figure 25). As it is illustrated that 85% of the sample has a diameter range (703–808 µm) which indicates the sample has a narrow size distribution.

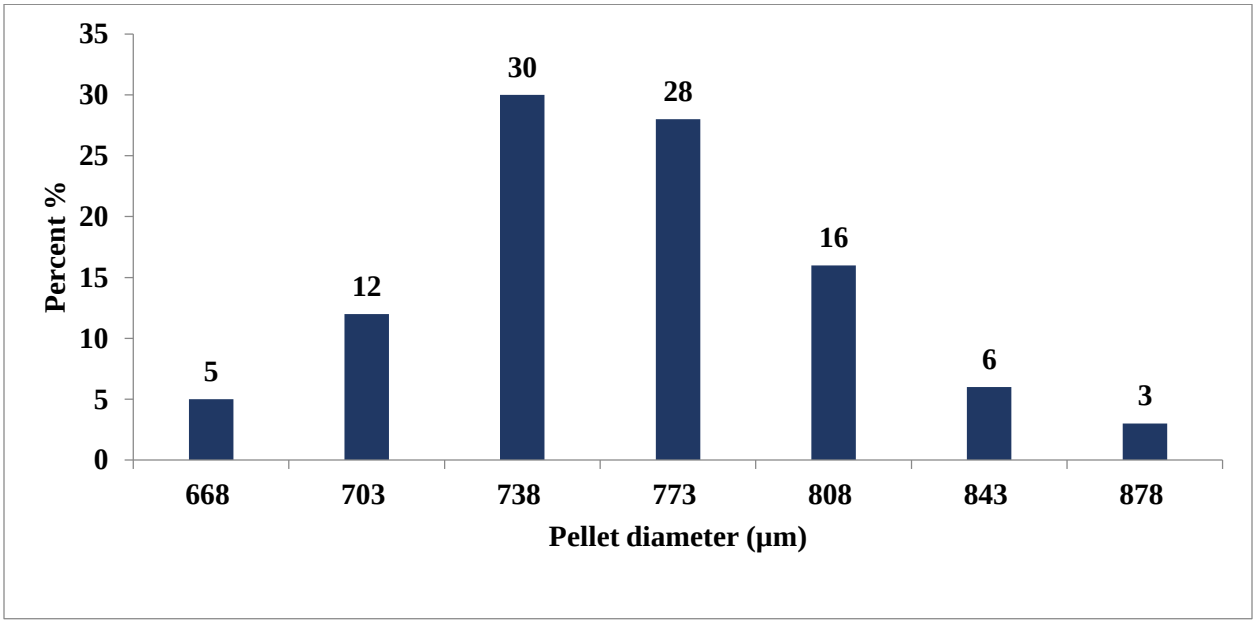


Figure 25: Pseudoephedrine hydrochloride pellets size distribution by image j® software

III. Pellets yield

Pellets yield by sieve analysis for 600-850 µm were depicted in (Figure 26) and its wonderful (79.14%)

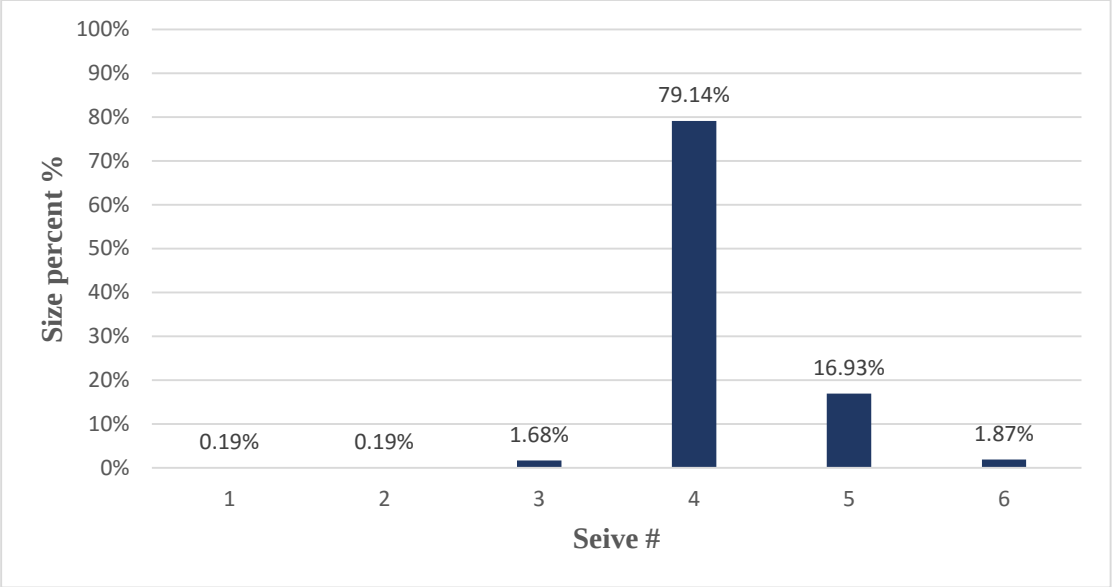


Figure 26: Results of pseudoephedrine hydrochloride pellets yield

IV. Moisture content

The scale directly reported the % weight loss due to moisture loss. Pseudoephedrine hydrochloride L.O.D = 5.83 is an acceptable value, high moisture content deteriorate disintegration.

V. Friability

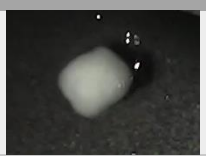
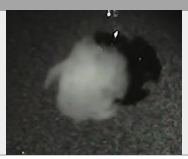
The test was performed by the friabilator. Friability was estimated to be 0.65% that is considered within acceptable limits (less than 1%). See appendix B

VI. Camera capture of the pellet disintegration process

The disintegration process was evaluated at room temperature under a static situation. And the camera captured images every 30 seconds as depicted in (Table 28), properly illustrating that Pseudoephedrine hydrochloride pellets began to explode into many pieces of loosely linked particles within 120 s, which easily separated under the oscillating motion of the USP disintegration equipment. The photos are compatible with the above-mentioned results from the

USP disintegration device. With a temperature increase to 37 °C, the disintegration caused the split into tiny fragments.

Table 28: Camera capture of pseudoephedrine hydrochloride pellet disintegration at a different time interval

Pellet #	0 sec	30 sec.	60 sec.	90 sec.	120 sec.
CPP4					

sec.: Second

VII. Drug content

The drug content of pellets was determined by measuring the absorbance of a specific weight of pellets and calculating the concentration using the linearity equation.

The drug content was → API % = 31.8 % of pellets weight. See Appendix D

VIII. Drug dissolution

Dissolution studies in the USP II paddle apparatus (see appendix F) revealed that the Pseudoephedrine hydrochloride pellets preparation released more than 95% of its drug in less than 20 minutes, indicating that the prepared fast-dissolving pellets tend to improve the drug release profile, and the disintegration modes reflect the pellets' dissolution characteristics. That is attributed to inclusion of soluble filler mannitol and utilizing the solubilizing power of the hydrophilic polymer PEG 400 results in a more porous matrix that facilitates water entry and rapid swelling, complemented by the wicking effect of a combination of disintegrants, which avoids slow diffusion from the insoluble matrix of MCC pellets.

The average of Pseudoephedrine hydrochloride release at each time point and its RSD is shown in (Table 29).

Table 29: Average release and RSD for pseudoephedrine hydrochloride

Time	Average	RSD
5.00	92.75	0.28
10.00	94.74	0.76
20.00	97.84	0.94
30.00	98.31	0.88
45.00	99.27	0.84
60.00	99.68	0.72

RSD: Relative standard deviation

The release profiles of pseudoephedrine hydrochloride are shown in (Figure 27).

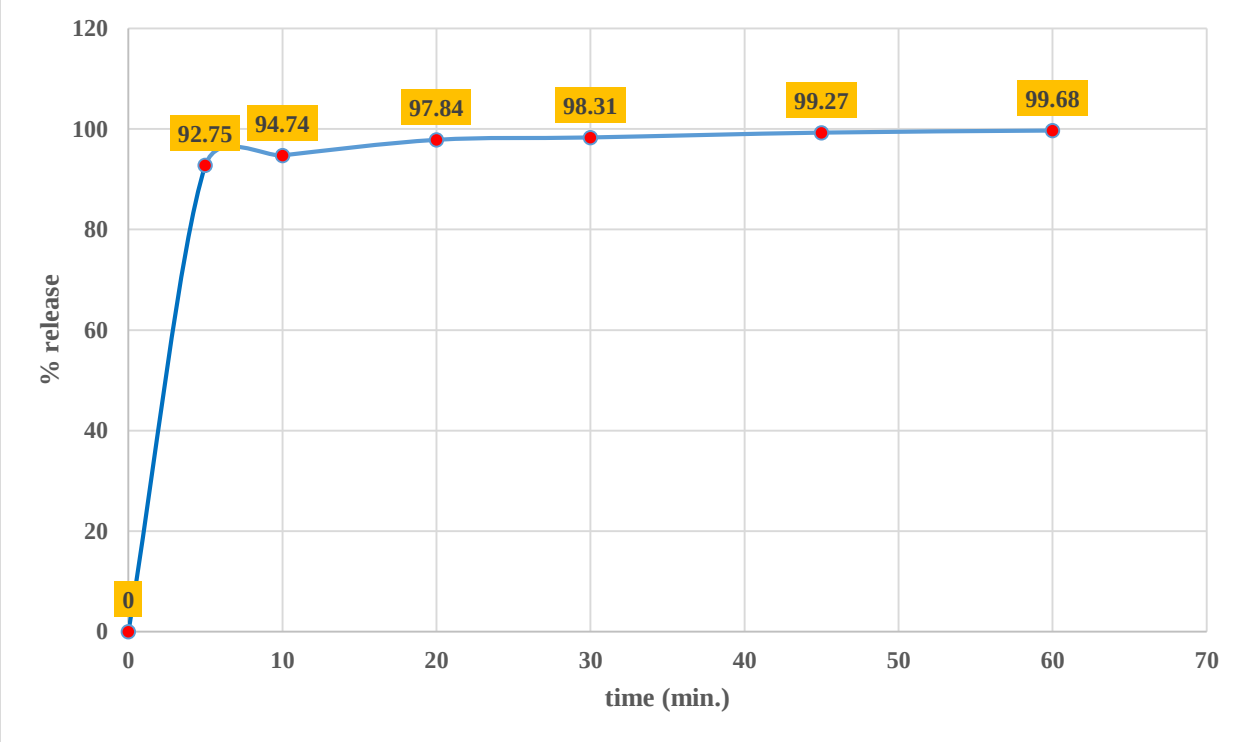


Figure 27: Pseudoephedrine hydrochloride dissolution profile

4.2.6.2. Orphenadrine citrate

Orphenadrine citrate was used as a second model drug, which is sparingly soluble in water. The DT of several batches is shown in (Table 12 and 30), as the formulation used offers a desirable shape and fast DT.

Table 30: Stage 1 and 2 results of the pellets formulation with orphenadrine citrate

Formula #	S. time	S. load	speed	Microscopic image	Roundness			Pass /fail	DT	Pass /fail
					Pellet #					
					1	2	3			
CPO1	30 sec.	15gm	3000 RPM		0.805	0.930	0.830	Pass	< 8 min.	Pass
CPO2	30 sec.	15gm	3000 RPM		0.944	0.933	0.855	Pass	<8 min.	Pass
CPO3	30 sec.	15gm	3000 RPM		0.900	0.957	0.960	Pass	< 8 min.	Pass
CPO4	30 sec.	15gm	3000 RPM		0.853	0.948	0.874	Pass	< 8 min.	Pass

S. time: Spheronization time, S. load: Spheronization load, DT: Disintegration time, min.:Minute.

I. Particle size distribution

The results of particle size distribution for formula CPO4 are shown in (Table 31). The test was performed by a sieve shaker. The outcomes revealed that the majority (70.35%) of the CPO4 batch pellets ranged from 600 to 850 µm. As a consequence, this size fraction was chosen for further study. Pellets usually come in the size range of 0.5-2 mm [6].

Table 31: Results of orphenadrine citrate pellets size distribution by sieve analysis

Mesh size number	Sieve #	mesh size (µm)	weight retained on each sieve (g)	Percent retained on each sieve (%)	Cumulative percent retained on each sieve (%)	Percentage passing (%)
16	6	1180	0.05	1.18	1.18	98.82
20	5	850	0.7	16.47	17.65	82.35
30	4	600	2.99	70.35	88.00	12.00
40	3	425	0.39	9.18	97.18	2.82
60	2	250	0.08	1.88	99.06	0.94
Pan	1	------	0.04	0.94	100	00

µm: Micrometer, g: Gram.

% retained = (Weight of pellets retained over x# sieve/Actual weight of pellets) *100

Pellets weight = 4.25 gm

As shown in (Figure 28) 10% of the sample is smaller than 561.9 µm, 50% is smaller than 735 µm, and 90% is smaller than 1003.2 µm

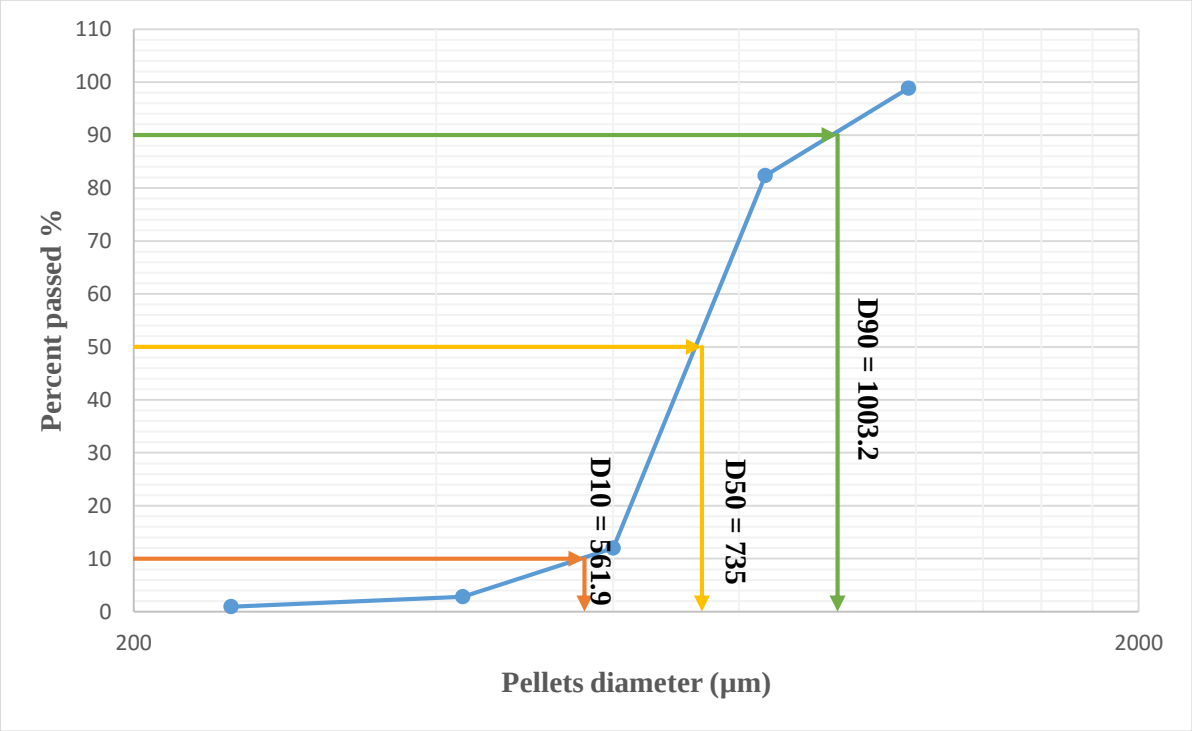


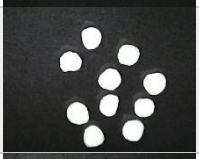
Figure 28: Orphenadrine citrate pellets size distribution by sieve analysis

II. Size and shape analysis by image j®

The results of size and shape analysis are shown in (Table 32). The test was performed by image j free software. The pellets in the majority of the CPO4 batch were approximately spherical with a roundness range between (0.87-.91).

All pellet formulations have an aspect ratio in the range of 1.09–1.15, which is within the limit (an aspect ratio of 1.00 denotes an ideal spherical shape; in practice, values up to 1.2 are allowed) [15].

Table 32: Results of orphenadrine citrate size and shape analysis

Pellet group #	Average Area = R2 π (µm2)	A/ π	R = SQRT (A/ π)	D (µm) = R*2	P.	F.D. (µm)	C.	AR	RN.	Microscopic image
1	523524	166643	408	816	2730	897	0.88	1.12	0.90	
2	482842	153693	392	784	2622	869	0.88	1.15	0.87	
3	523097	166507	408	816	2723	879	0.89	1.10	0.91	
4	484375	154181	393	785	2620	850	0.88	1.10	0.91	
5	522031	166168	408	815	2734	892	0.88	1.11	0.90	
6	491335	156397	395	791	2658	863	0.87	1.09	0.92	
7	458107	145820	382	764	2558	848	0.88	1.14	0.88	
8	436906	139071	373	746	2514	836	0.87	1.12	0.90	
9	410304	130604	361	723	2430	798	0.87	1.13	0.89	
10	410304	130604	361	723	2430	798	0.87	1.13	0.89	

A: Area., SQRT: Square root, D: Diameter, R: Radius F. D.: Ferret diameter, P: Perimeter, C: Circularity, AR: Aspect ratio, RN.: Roundness

Pellet size distribution for formula CPO4 derived from estimated pellet diameter from image J® software is shown in (Figure 29). As it is illustrated that 84% of the sample has a diameter range (724–829 µm) which indicates the sample has a narrow size distribution.

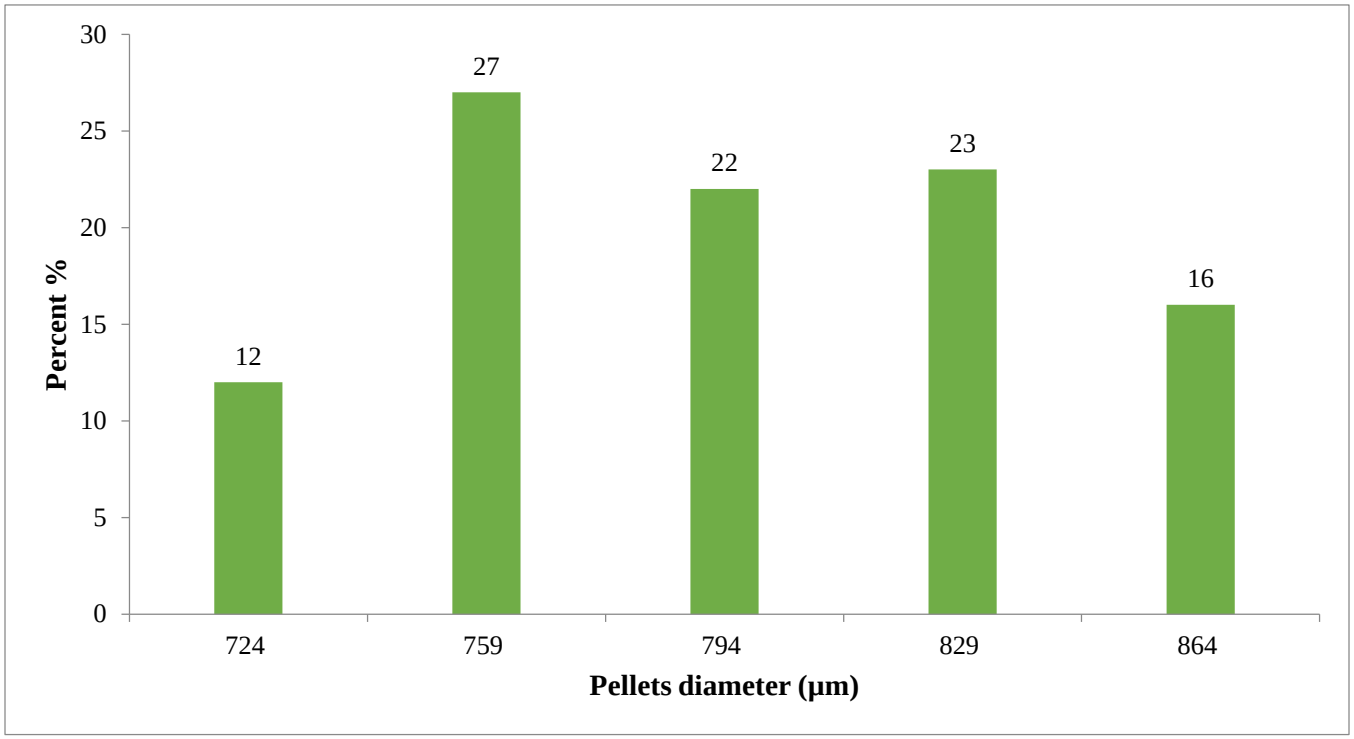


Figure 29: Orphenadrine citrate pellets size distribution by image j® software

III. Pellets yield

Pellets yield by sieve analysis for 600-850 µm were depicted in (Figure 30) and its satisfactory (70.35%)

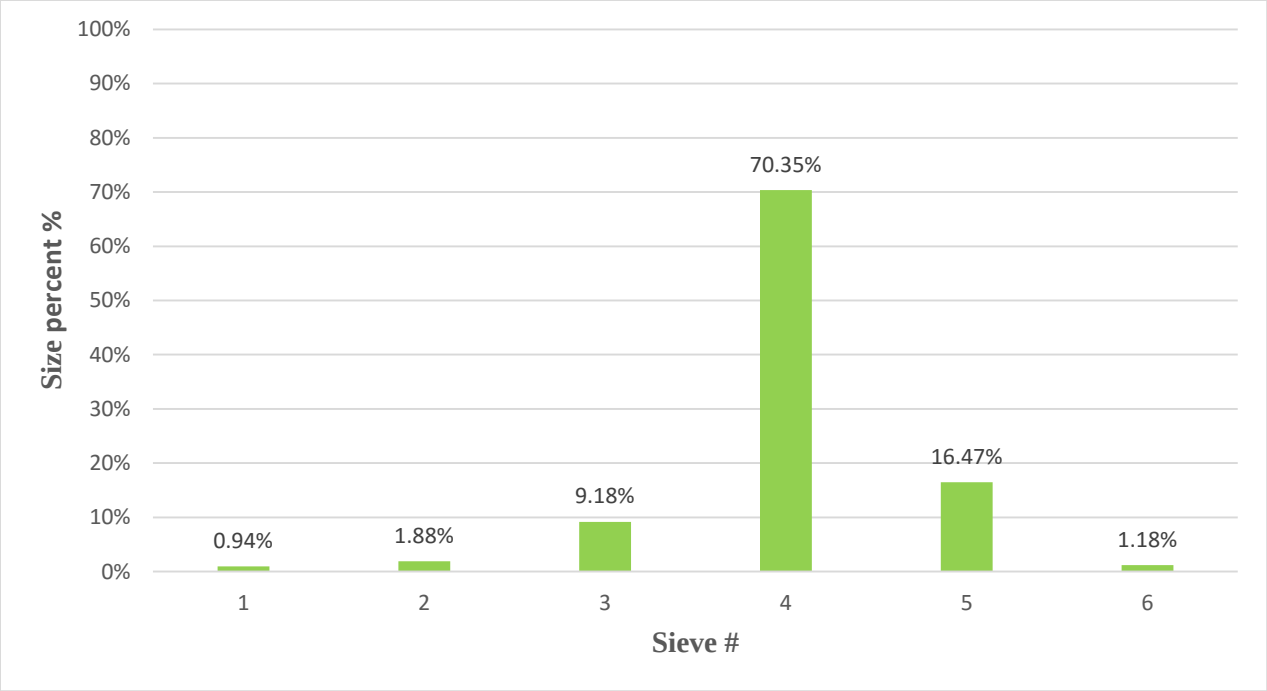


Figure 30: Results of orphenadrine citrate pellets yield

IV. Moisture content

The scale directly reported the % weight loss due to moisture loss. Orphenadrine citrate L.O.D = 5.36 is an acceptable value, high moisture content deteriorate disintegration.

V. Friability

The test was performed by the friabilator. Friability was estimated to be 0.71% that is considered within acceptable limits (less than 1%). See appendix C

VI. Camera capture of the pellet disintegration process

The disintegration process was evaluated at room temperature under a static situation. And the camera captured images every 30 seconds (Table 33), properly illustrating that Orphenadrine citrate pellets began to swell and cracks start to appear after 120 s, which easily separated under

the oscillating motion of the USP disintegration equipment. The photos are compatible with the above-mentioned results from the USP disintegration device. With a temperature increase to 37 °C, the disintegration caused the split into tiny fragments.

Table 33: Camera capture of orphenadrine citrate pellets at different time interval

Pellet #	0 sec.	30 sec.	60 sec.	90 sec.	120 sec.
CPO4					

sec.: Second

VII. Drug content

The drug content of pellets was determined by measuring the absorbance of a specific weight of pellets and calculating the concentration using the linearity equation.

The drug content was → API % = 32.1 % of pellets weight. See appendix E

VIII. Drug dissolution

Dissolution studies in the USP II paddle apparatus (see appendix G) revealed that the orphenadrine citrate pellets preparation released more than 90% of its drug in less than 20 minutes, (Figure 31) indicating that the prepared fast-dissolving pellets tend to improve the drug release profile, and the disintegration modes reflect the pellets' dissolution characteristics. That is attributed to inclusion of soluble filler mannitol and utilizing the solubilizing power of the hydrophillic polymer PEG 400 results in a more porous matrix that facilitates water entry and rapid swelling, complemented by the wicking effect of a combination of disintegrants, which avoids slow diffusion from the insoluble matrix of MCC pellets.

The average of Orphenadrine citrate release at each time point and its RSD is shown in (Table 34).

Table 34: Average release and RSD for orphenadrine citrate

Time	Average	RSD
5	61.10	2.73
10	85.76	0.92
20	90.44	0.99
30	94.27	0.99
45	94.92	1.00
60	97.31	0.97

RSD: Relative standard deviation

The release profiles of Orphenadrine citrate are shown in (Figure 31).

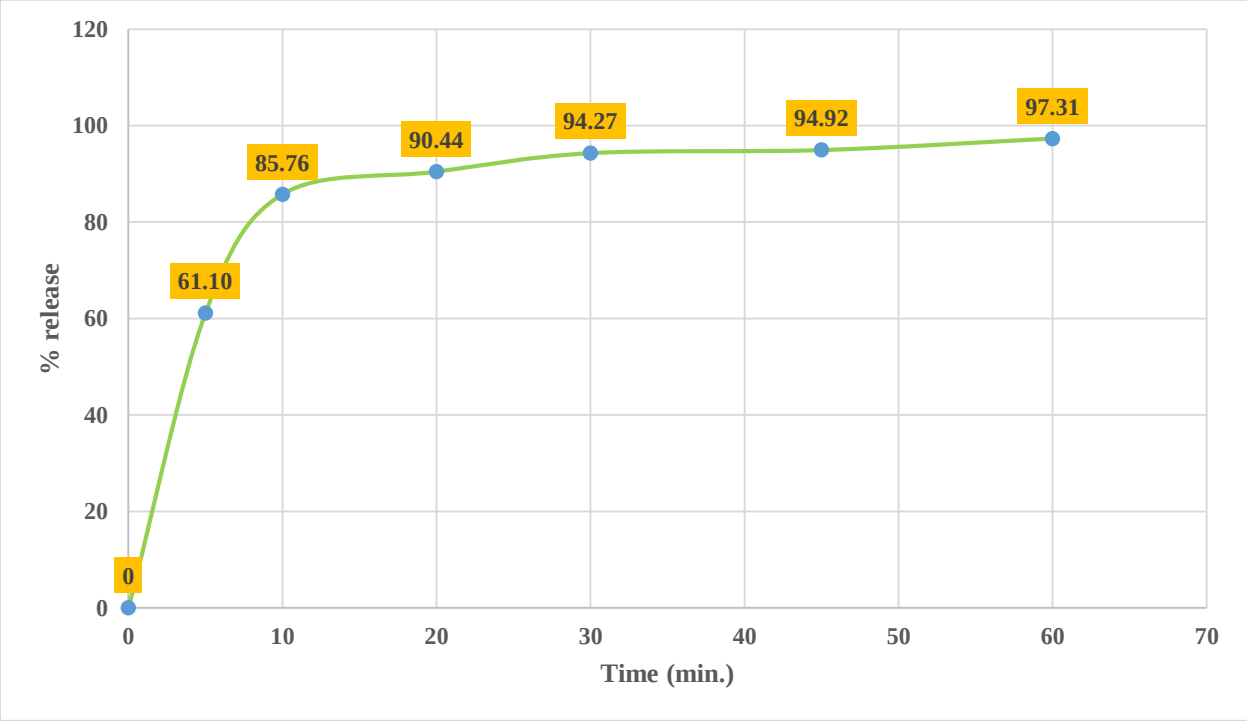


Figure 31: Orphenadrine citrate dissolution profile

The results indicate that the disintegrating MCC pellets are useful for improving drug dissolution of pseudoephedrine hydrochloride and orphenadrine citrate The composition of pellets had a significant effect on the disintegration time of all formulations. Both the hydrophilicity of PEG and the solubility of mannitol had a limited ability to disintegrate the matrix of pellets, but when combined with CCS and PPXL, they increased pellet disintegration by swelling and wetting of the

pellet core. The combination of these approaches has a synergistic effect on pellet formation, overcoming the problem of drug disintegration in extruded MCC pellets [71]. While the difference in disintegration time and dissolution between pseudoephedrine hydrochloride and orphenadrine citrate could be attributed to the amount of water required for granulation. Orphenadrine citrate needed much water compared with pseudoephedrine hydrochloride. These findings are confirmed by a study that demonstrated that the optimal water level was lowered as the drug's water solubility increased due to the loss of the drug by solvation [30], and L. Baert research, who noticed that when more granulation liquid was used, the release was slower. The slower rate of release was linked to an increase in the pellets' hardness and density [28].

Chapter V: Conclusion

5. Conclusion

Extrusion-spheronization is a multistage technique for producing uniformly sized pellets from wet granules. The complex interaction between equipment, formulation, and process variables, as well as technical knowledge and researcher experience, is critical to the success of these procedures.

Fast disintegrating pellets were successfully designed and optimized. New formulations of placebo MCC PH 101-based pellets with fast disintegrating characteristics were evolved by extrusion and spheronization. The incorporation of soluble filler mannitol, hydrophilic polymer PEG 400, with a super-disintegrant CCS, and PPXL permitted the pellets to explode and disintegrate within a very short time. The results revealed that the chosen formula gives the pellets a spherical shape, strength, and integrity. Then, uploading of model drugs and evaluation of their drug dissolution were also greatly improved. Fast dissolution of freely soluble drugs like pseudoephedrine hydrochloride and sparingly soluble drugs like orphenadrine citrate was achieved due to pellet disintegration (>90% drug release in 20 minutes). The findings indicate that the disintegrating MCC pellets are useful for improving drug dissolution. Final pellet evaluation confirmed producing pellets that have a high process yield (70%–80%), good pellet sphericity (<AR 1.2), low friability (<1%), and quick disintegration (less than 10 minutes).

Multiparticulate systems are one of the best dosage forms for children, especially from the pre-school years and above, while the use of orodispersible pellets could expand their use to younger kids, such as infants and toddlers. Pellets are being investigated for a wide range of applications, including the immediate and modified release of drugs, implants, orally dispersible preparations, effervescent medicines, and solid dispersions. Established APIs can be reformed into pellets by employing the advantages of their inherent properties and flexibility.

Reference

[1] A. Farmoudeh, A. Rezaeiroshan, M. Abbaspour, A. Nokhodchi, and P. Ebrahimnejad, "Solid Dispersion Pellets: An Efficient Pharmaceutical Approach to Enrich the Solubility and Dissolution Rate of Deferasirox," *Biomed Res. Int.*, vol. 2020, 2020, doi: 10.1155/2020/8583540.

[2] D. Weis, M. Evers, M. Thommes, and S. Antonyuk, "DEM simulation of the mixing behavior in a spheronization process," *Chem. Eng. Sci.*, vol. 192, no. July, pp. 803–815, 2018, doi: 10.1016/j.ces.2018.07.057.

[3] N. Shah, T. Mehta, and M. Gohel, "Formulation and Optimization of Multiparticulate Drug Delivery System Approach for High Drug Loading," *AAPS PharmSciTech*, vol. 18, no. 6, pp. 2157–2167, 2017, doi: 10.1208/s12249-016-0689-6.

[4] M. A. Ibrahim, G. M. Zayed, F. M. Alsharif, and W. A. Abdelhafez, "Utilizing mixer torque rheometer in the prediction of optimal wet massing parameters for pellet formulation by extrusion/spheronization," *Saudi Pharm. J.*, vol. 27, no. 2, pp. 182–190, 2019, doi: 10.1016/j.jsps.2018.10.002.

[5] H. Afrasiabi Garekani, S. F. Aftabi, F. F. Nia, M. Javidi, A. Nokhodchi, and F. Sadeghi, "Synergistic effect of polyethylene glycol and superdisintegrant on dissolution rate enhancement of simvastatin in pellet formulation," *Pharm. Dev. Technol.*, vol. 24, no. 6, pp. 720–728, 2019, doi: 10.1080/10837450.2019.1584632.

[6] D. M. Parikh, *Handbook of pharmaceutical granulation technology*. 2005.

[7] S. N. Politis and D. M. Rekkas, "Pelletization Processes for Pharmaceutical Applications: A Patent Review," *Recent Pat. Drug Deliv. Formul.*, vol. 5, no. 1, pp. 61–78, 2011, doi: 10.2174/187221111794109493.

[8] P. Kleinebudde, M. Schröder, P. Schultz, B. W. Müller, T. Waaler, and L. Nymo, "Importance of the fraction of microcrystalline cellulose and spheronization speed on the properties of extruded pellets made from binary mixtures," *Pharm. Dev. Technol.*, vol. 4, no. 3, pp. 397–404, 1999, doi: 10.1081/PDT-100101375.

[9] H. P. Patel, J. K. Patel, R. R. Patel, and M. P. Patel, "PELLETS : A GENERAL OVERVIEW," vol. 02, no. 6, pp. 21–31, 2010.

[10] M. D. Köster, "Spheronization Process - Particle Kinematics and Pellet Formation Mechanisms," *PhD Diss. - Düsseld.*, p. 118, 2012.

[11] T. Trinh and L. Nguyen, "Extrusion- spheronization of pharmaceutical products : To cite this version :https://tel.archives-ouvertes.fr/tel-01756974/document," 2018.

[12] V. R. Sinha, M. K. Agrawal, A. Agarwal, G. Singh, and D. Ghai, "Extrusion-spheronization: Process variables and characterization," *Crit. Rev. Ther. Drug Carrier Syst.*, vol. 26, no. 3, pp. 275–331, 2009, doi: 10.1615/CritRevTherDrugCarrierSyst.v26.i3.20.

[13] V. A. Saharan, *Current Advances in Drug Delivery Through Fast Dissolving/Disintegrating Dosage Forms.* Bentham Science Publishers, 2017.

[14] T. H. Hoang Thi, S. Lhafidi, S. P. Carneiro, and M. P. Flament, "Feasability of a new process to produce fast disintegrating pellets as novel multiparticulate dosage form for pediatric use," *Int. J. Pharm.*, vol. 496, no. 2, pp. 842–849, 2015, doi: 10.1016/j.ijpharm.2015.09.049.

[15] B. Chamsai and P. Sriamornsak, "Novel disintegrating microcrystalline cellulose pellets with improved drug dissolution performance," *Powder Technol.*, vol. 233, pp. 278–285, 2013, doi: 10.1016/j.powtec.2012.08.019.

[16] H. Kranz, K. Jürgens, M. Pinier, and J. Siepmann, "Drug release from MCC- and carrageenan-based pellets: Experiment and theory," *Eur. J. Pharm. Biopharm.*, vol. 73, no. 2, pp. 302–309, 2009, doi: 10.1016/j.ejpb.2009.05.007.

[17] C. Souto, A. Rodríguez, S. Parajes, and R. Martínez-Pacheco, "A comparative study of the utility of two superdisintegrants in microcrystalline cellulose pellets prepared by extrusion-spheronization," *Eur. J. Pharm. Biopharm.*, vol. 61, no. 1–2, pp. 94–99, 2005, doi: 10.1016/j.ejpb.2005.04.003.

[18] C. Vervaet, L. Baert, and J. P. Remon, "Enhancement of in vitro drug release by using polyethylene glycol 400 and PEG-40 hydrogenated caVervaet, C., Baert, L., & Remon, J. P. (1994).," *Int. J. Pharm.*, vol. 108, no. 3, pp. 207–212, 1994, doi: 10.1016/0378-5173(94)90129-5.

[19] F. O. Costa, A. A. C. C. Pais, and J. J. S. Sousa, "Analysis of formulation effects in the dissolution of ibuprofen pellets," *Int. J. Pharm.*, vol. 270, no. 1–2, pp. 9–19, 2004, doi: 10.1016/j.ijpharm.2003.10.002.

[20] M. Levin, "Pharmaceutical Process Scale-Up, Secon Edition," 2006.

[21] M. P. Bryan, M. D. Kent, J. Rickenbach, G. Rimmer, D. I. Wilson, and S. L. Rough, "The effect of mixing on the extrusion-spheronisation of a micro-crystalline cellulose paste," *Int. J. Pharm.*, vol. 479, no. 1, pp. 1–10, 2015, doi: 10.1016/j.ijpharm.2014.12.028.

[22] M. Zhang, Y. Li, J. F. Xing, S. L. Rough, and D. I. Wilson, "Influence of plate surface protuberance size and shape on the production of pellets by extrusion-spheronisation," *Chem. Eng. Res. Des.*, vol. 109, pp. 97–107, 2016, doi: 10.1016/j.cherd.2016.01.004.

[23] J. J. Sousa, A. Sousa, F. Podczeck, and J. M. Newton, "Factors influencing the physical characteristics of pellets obtained by extrusion-spheronization," *Int. J. Pharm.*, vol. 232, no. 1–2, pp. 91–106, 2002, doi: 10.1016/S0378-5173(01)00908-5.

[24] A. Dukić-Ott, C. Vervaet, and J. P. Remon, "Ghent Uni Versity Faculty of Pharmaceutical Sciences Laboratory of Pharmaceutical Technology Modified Starch As an Excipient for Pellets Prepared By Means of Extrusion/Spheronisation," 2008.

[25] N. Yadav and A. Verma, "Pharmaceutical pellets: A versatile carrier for oral controlled delivery of drugs," *Indian J. Pharm. Educ. Res.*, vol. 50, no. 3, pp. S146–S160, 2016, doi: 10.5530/ijper.50.3.27.

[26] C. Londoño and J. Rojas, “Using a Multivariate Analysis,” *Thai J. Pharm. Sci.*, vol. 41, no. 2, pp. 69–75, 2017.

[27] G. Tomer, F. Podczeck, and J. M. Newton, “The influence of type and quantity of model drug on the extrusion/spheronization of mixtures with microcrystalline cellulose - I. Extrusion parameters,” *Int. J. Pharm.*, vol. 217, no. 1–2, pp. 237–248, 2001, doi: 10.1016/S0378-5173(01)00611-1.

[28] L. Baert and J. P. Remon, “Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion spheronisation,” *Int. J. Pharm.*, vol. 95, no. 1–3, pp. 135–141, 1993, doi: 10.1016/0378-5173(93)90400-A.

[29] J. Varshosaz, R. A. Kennedy, and E. M. Gipps, “Effect of binder level and granulating liquid on phenylbutazone pellets prepared by extrusion-spheronization,” *Drug Dev. Ind. Pharm.*, vol. 23, no. 6, pp. 611–618, 1997, doi: 10.3109/03639049709149828.

[30] E. M. Theismann, J. K. Keppler, M. Owen, K. Schwarz, and W. Schlindwein, “Modelling the effect of process parameters on thewet extrusion and spheronisation of high-loaded nicotinamide pellets using a quality by design approach,” *Pharmaceutics*, vol. 11, no. 4, 2019, doi: 10.3390/pharmaceutics11040154.

[31] J. Chatchawalsaisin, F. Podczeck, and J. M. Newton, “The preparation by extrusion/spheronization and the properties of pellets containing drugs, microcrystalline cellulose and glyceryl monostearate,” *Eur. J. Pharm. Sci.*, vol. 24, no. 1, pp. 35–48, 2005, doi: 10.1016/j.ejps.2004.09.008.

[32] S. Sarkar, “Studies on Pellet Composition and Formation in Extrusion-Spheronization,” p. Jadavpur, 2012.

[33] H. Michie, F. Podczeck, and J. Michael, “The influence of plate design on the properties of pellets produced by extrusion and spheronization,” *Int. J. Pharm.*, vol. 434, no. 1–2, pp. 175–182, 2012, doi: 10.1016/j.ijpharm.2012.05.050.

[34] R. V. Mishra, S. G. Paldewar, and T. D. Nandgude, “An outline of variables in pelletization by extrusion and spheronization,” *Int. J. Appl. Pharm.*, vol. 12, no. 4, pp. 39–44, 2020, doi: 10.22159/ijap.2020v12i4.37277.

[35] N. Jadhav, M. Gade, N. Salunkhe, and A. Paradkar, “Extrusion-Spheronization of Talc using Microcrystalline Cellulose as a Pellet Aid: Part I,” *J. Pharm. Innov.*, vol. 9, no. 4, pp. 321–330, 2014, doi: 10.1007/s12247-014-9197-y.

[36] D. Hegyesi *et al.*, “Preparation and physicochemical characterization of matrix pellets containing APIs with different solubility via extrusion process,” *Drug Dev. Ind. Pharm.*, vol. 43, no. 3, pp. 458–464, 2017, doi: 10.1080/03639045.2016.1261150.

[37] D. S. S. and P. A. R., “Formulation and Optimization of Immediate Release Pellets of Antiplatelet Drugs Using Design of Experimentation,” *Int. J. Drug Deliv. Technol.*, vol. 7, no. 04, 2017, doi: 10.25258/ijddt.v7i04.10648.

[38] C. Krueger, M. Thommes, and P. Kleinebudde, “Spheronisation mechanism of MCC II-based pellets,” *Powder Technol.*, vol. 238, pp. 176–187, 2013, doi: 10.1016/j.powtec.2011.12.052.

[39] A. B. Bashaiwoldu, F. Podczeck, and J. M. Newton, “A study on the effect of drying techniques on the mechanical properties of pellets and compacted pellets,” *Eur. J. Pharm. Sci.*, vol. 21, no. 2–3, pp. 119–129, 2004, doi: 10.1016/j.ejps.2003.09.013.

[40] I. Alves-Silva, R. N. Marreto, G. M. Gelfuso, L. C. L. Sá-Barreto, E. M. Lima, and M. S. S. Cunha-Filho, “Preparation of benznidazole pellets for immediate drug delivery using the extrusion spheronization technique,” *Drug Dev. Ind. Pharm.*, vol. 43, no. 5, pp. 762–769, 2017, doi: 10.1080/03639045.2016.1220574.

[41] J. C. Wlosnewski, M. Kumpugdee-Vollrath, and P. Sriamornsak, “Effect of drying technique and disintegrant on physical properties and drug release behavior of microcrystalline cellulose-based pellets prepared by extrusion/spheronization,” *Chem. Eng. Res. Des.*, vol. 88, no. 1, pp. 100–108, 2010, doi: 10.1016/j.cherd.2009.07.001.

[42] V. S. and V. R. Kammili Lavanya*, “PELLETIZATION TECHNOLOGY: A QUICK REVIEW.” [Online]. Available: http://ijpsr.com/bft-article/pelletization-technology-a-quick-review/?view=fulltext.

[43] S. P. Jain, P. Pal Singh, and P. D. Amin, “Alternative extrusionspheronization aids,” *Drug Dev. Ind. Pharm.*, vol. 36, no. 11, pp. 1364–1376, 2010, doi: 10.3109/03639045.2010.482590.

[44] A. Dukić-Ott, M. Thommes, J. P. Remon, P. Kleinebudde, and C. Vervaet, “Production of pellets via extrusion-spheronisation without the incorporation of microcrystalline cellulose: A critical review,” *Eur. J. Pharm. Biopharm.*, vol. 71, no. 1, pp. 38–46, 2009, doi: 10.1016/j.ejpb.2008.08.005.

[45] I. Tho, P. Kleinebudde, and S. A. Sande, “Extrusion/spheronization of pectin-based formulations. I. Screening of important factors,” *AAPS PharmSciTech*, vol. 2, no. 4, pp. 1–9, 2001, doi: 10.1007/BF02830566.

[46] A. Dukić-Ott, J. P. Remon, P. Foreman, and C. Vervaet, “Immediate release of poorly soluble drugs from starch-based pellets prepared via extrusion/spheronisation,” *Eur. J. Pharm. Biopharm.*, vol. 67, no. 3, pp. 715–724, 2007, doi: 10.1016/j.ejpb.2007.04.014.

[47] U. Arora, V. Thakkar, L. Baldaniya, and M. C. Gohel, “Fabrication and evaluation of fast disintegrating pellets of cilostazol,” *Drug Dev. Ind. Pharm.*, vol. 46, no. 12, pp. 1927–1946, 2020, doi: 10.1080/03639045.2020.1826509.

[48] I. Moore, *Pharmaceutical excipients*, vol. 79, no. 4. 2017.

[49] S. Zhang, Y. Xia, H. Yan, Y. Zhang, W. Zhang, and J. Liu, “The water holding ability of powder masses: Characterization and influence on the preparation of pellets via extrusion/spheronization,” *Powder Technol.*, vol. 301, pp. 940–948, 2016, doi: 10.1016/j.powtec.2016.07.030.

[50] A. Goyanes, C. Souto, and R. Martínez-Pacheco, “Control of drug release by incorporation of sorbitol or mannitol in microcrystalline-cellulose-based pellets prepared by extrusion-spheronization,” *Pharm. Dev. Technol.*, vol. 15, no. 6, pp. 626–635, 2010, doi: 10.3109/10837450903419653.

[51] M. Ibrahim, G. M. Mahrous, and F. Alanazi, “Indomethacin-Loaded Pellets Prepared by

Extrusion / Spheronization : Effect of cosolvents indomethacin- loaded pellets prepared by extrusion / spheronization.," no. March 2019, 2011.

[52] I. Ghebre-Sellassie, *multiparticulate oral drug delivery*. 4751.

[53] C. Lustig-Gustafsson, H. Kaur Johal, F. Podczeck, and J. M. Newton, "The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation," *Eur. J. Pharm. Sci.*, vol. 8, no. 2, pp. 147–152, 1999, doi: 10.1016/S0928-0987(99)00004-4.

[54] G. P. Millili and J. B. Schwartz, "The strength of microcrystalline cellulose pellets: The effect of granulating with water/ethanol mixtures," *Drug Dev. Ind. Pharm.*, vol. 16, no. 8, pp. 1411–1426, 1990, doi: 10.3109/03639049009115970.

[55] Z. V. Bvg, "hand book of pharmaceutical excipient," 2009.

[56] S. P. Jain, D. C. Mehta, S. P. Shah, P. P. Singh, and P. D. Amin, "Melt-in-mouth pellets of fexofenadine hydrochloride using crospovidone as an extrusion-spheronisation aid," *AAPS PharmSciTech*, vol. 11, no. 2, pp. 917–923, 2010, doi: 10.1208/s12249-010-9443-7.

[57] V. Kunam, V. Suryadevara, D. R. Garikapati, V. B. R. Mandava, and R. Sasidhar, "Solubility and dissolution rate enhancement of ezetimibe by solid dispersion and pelletization techniques using soluplus as carrier," *Int. J. Appl. Pharm.*, vol. 11, no. 4, pp. 57–64, 2019, doi: 10.22159/ijap.2019v11i4.32274.

[58] M. A. Ibrahim and G. A. Shazly, "Evaluation of diclofenac sodium sustained release matrix pellets: Impact of polyethylene glycols molecular weight," *Acta Pol. Pharm. - Drug Res.*, vol. 72, no. 5, pp. 987–997, 2015.

[59] M. Fairstein, R. Swissa, and A. Dahan, "Regional-dependent intestinal permeability and BCS classification: Elucidation of pH-related complexity in rats using pseudoephedrine," *AAPS J.*, vol. 15, no. 2, pp. 589–597, 2013, doi: 10.1208/s12248-013-9462-x.

[60] L. Z. Benet, F. Broccatelli, and T. I. Oprea, "BDDCS applied to over 900 drugs," *AAPS J.*, vol. 13, no. 4, pp. 519–547, 2011, doi: 10.1208/s12248-011-9290-9.

[61] "USP-NF description," p. 4846, 2021.

[62] Steven A. Benezra and John W. McRae, "Pseudoephedrine-hydrochloride." [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/Pseudoephedrine-hydrochloride.

[63] C. Formula and M. Weight, "Latest Revision: June 22, 2005."

[64] pubchem, "orphenadrine citrate," *https://pubchem.ncbi.nlm.nih.gov/compound/Orphenadrine-citrate*. [Online]. Available: https://pubchem.ncbi.nlm.nih.gov/compound/Orphenadrine-citrate.

[65] A. K. F. Jumaa, A. A. Abdulrasool, and H. A. Al Dujali, "Received 5-8-2001 Accepted 11-6-2002 Formulation and Clinical Evaluation of Orphenadrine citrate as a Plain Tablet," vol. 15, no. 1, pp. 1–9, 2006.

[66] M. S. E. Qurt, "Preparation of topical Orphenadrine citrate and investigating the Effect of different penetration enhancers on drug permeation rate," no. 57, p. 3, 2009.

[67] “Alfonso R. Gennaro - Remington_ The Science And Practice Of Pharmacy -Lippincott Williams & Wilkins (2005).pdf.” 2005.

[68] E. Gryczová, K. Dvořáčková, and M. Rabiškova, “Evaluation of pellet friability,” *Ces. a Slov. Farm.*, vol. 58, no. 1, pp. 9–13, 2009.

[69] S. Mehta, T. De Beer, J. P. Remon, and C. Vervaet, “Effect of disintegrants on the properties of multiparticulate tablets comprising starch pellets and excipient granules,” *Int. J. Pharm.*, vol. 422, no. 1–2, pp. 310–317, 2012, doi: 10.1016/j.ijpharm.2011.11.017.

[70] Y. Xia, C. Y. Shi, J. G. Fang, and W. Q. Wang, “Approaches to developing fast release pellets via wet extrusion-spheronization,” *Pharm. Dev. Technol.*, vol. 23, no. 5, pp. 432–441, 2018, doi: 10.1080/10837450.2016.1265556.

[71] P. M. Desai, P. X. H. Er, C. V. Liew, and P. W. S. Heng, “Functionality of disintegrants and their mixtures in enabling fast disintegration of tablets by a quality by design approach,” *AAPS PharmSciTech*, vol. 15, no. 5, pp. 1093–1104, 2014, doi: 10.1208/s12249-014-0137-4.

[72] D. Markl and J. A. Zeitler, “A Review of Disintegration Mechanisms and Measurement Techniques,” *Pharm. Res.*, vol. 34, no. 5, pp. 890–917, 2017, doi: 10.1007/s11095-017-2129-z.

[73] USP, “pseudoephedrine.pdf.” 2017.

[74] USP, “orphenadrine.pdf.” 2017.

Appendix

Appendix A: CP12 friability calculations

The friability test results are as follows:

$$Friabilty = \frac{W1 - W2}{W1} * 100\%$$

$$Friability = \frac{11.6 - 11.53}{11.6}$$

$$CP12\ friability = 0.6\%$$

Appendix B: Pseudoephedrine hydrochloride friability calculation

The friability test results are as follows:

$$Friabilty = \frac{W1 - W2}{W1} * 100\%$$

$$Ps.HCl\ friability = \frac{10.69 - 10.62}{10.69}$$

$$Ps\ HCl\ friability = 0.65\%$$

Appendix C: Orphenadrine citrate friability calculation

The friability test results are as follows:

$$Friabilty = \frac{W1 - W2}{W1} * 100\%$$

$$Orpha.citrate\ friability = \frac{4.25 - 4.22}{4.25}$$

$$Orpha.citrate\ friability = 0.71\%$$

Appendix D: Pseudoephedrine hydrochloride drug content

The drug content of pellets was determined by measuring the absorbance of a specific weight of pellets and calculating the concentration using the linearity equation.

$$Y = 23.959X + 0.0137$$

Y= absorbance, X= concentration

Sample absorbance = 0.912 by applying in linearity equation

$$0.912 = 23.959X + 0.0137$$

→ Sample concentration = 0.037493218 mg/ml

→API quantity

$$API\ quantity = sample\ concentration * dilution\ factor$$

$$API\ quantity = 0.037493218 * \frac{20}{2} * 250$$

→ API quantity = 93.73304395 mg

API % =

$$API\% = \frac{API\ quantity}{pellets\ weight} * 100$$

$$API\% = \frac{93.73304395}{294.75} * 100$$

API % = 31.8 % of pellets weight

Appendix E: Orphenadrine citrate drug content

The drug content of pellets was determined by measuring the absorbance of a specific weight of pellets and calculating the concentration using the linearity equation.

$$Y = 43.388X + 0.0059$$

Y= absorbance, X= concentration

Sample absorbance = 0.779 by applying in linearity equation

$$0.779 = 43.388X + 0.0059$$

→ Sample concentration = 0.017818291 mg/ml

→API quantity

$$API\ quantity = sample\ concentration * dilution\ factor$$

$$API\ quantity = 0.017818291 * \frac{200}{5} * 1000$$

→ API quantity = 712.7316309

API % =

$$API\% = \frac{API\ quantity}{pellets\ weight} * 100$$

$$API\% = \frac{712.7316309}{2220.33} * 100$$

The drug content was → API % = 32.1 % of pellets weight.

Appendix F: Pseudoephedrine hydrochloride dissolution

The pellet weight in each chamber of the USP apparatus and the Pseudoephedrine hydrochloride quantity in each is depicted in (Table 35)

Table 35: Pseudoephedrine hydrochloride sample weight used in dissolution

Sample #	Pellets weight (mg)	API quantity
1.00	104.20	33.14
2.00	103.79	33.01
3.00	104.50	33.23
4.00	104.30	33.17
5.00	103.85	33.03
6.00	103.99	33.07

Mg: milligram, API: Active pharmaceutical ingredient

Dissolution of Pseudoephedrine hydrochloride from the pellet formulation in water was calculated and (Table 36) represent the quantity of drug released at each time point

Table 36: Pseudoephedrine hydrochloride dissolution calculations

Sample (Ps. HCl)	absorbance(nm)	Conc. (mg/ml) y = 23.959 x + 0.0137	Q (mg) (C1*900)	% Release (Q/API quantity)
SA1- 5 MIN	0.831	0.034	30.701	92.651
SA2- 5 MIN	0.829	0.034	30.626	92.789
SA3- 5 MIN	0.83	0.034	30.664	92.272
SA4- 5 MIN	0.833	0.034	30.776	92.788
SA5- 5 MIN	0.831	0.034	30.701	92.963
SA6- 5 MIN	0.833	0.034	30.776	93.065
SA1- 10 MIN	0.852	0.035	31.315	94.503
SA2- 10 MIN	0.849	0.035	31.203	94.537
SA3- 10 MIN	0.855	0.035	31.427	94.569
SA4- 10 MIN	0.856	0.035	31.465	94.863
SA5-10 MIN	0.855	0.035	31.427	95.161
SA6- 10 MIN	0.853	0.035	31.352	94.807
SA1- 20 MIN	0.885	0.036	32.366	97.338

SA2- 20 MIN	0.882	0.036	32.255	97.723
SA3- 20 MIN	0.885	0.036	32.366	97.394
SA4- 20 MIN	0.886	0.036	32.403	97.693
SA5- 20 MIN	0.889	0.037	32.515	98.454
SA6- 20 MIN	0.89	0.037	32.552	98.434
SA1- 30 MIN	0.899	0.037	32.701	98.687
SA2- 30 MIN	0.895	0.037	32.554	98.629
SA3-30 MIN	0.891	0.037	32.406	97.514
SA4- 30 MIN	0.895	0.037	32.554	98.147
SA5- 30 MIN	0.896	0.037	32.590	98.684
SA6- 30 MIN	0.893	0.037	32.480	98.216
SA1- 45 MIN	0.908	0.037	32.847	99.127
SA2- 45 MIN	0.91	0.037	32.921	99.741
SA3- 45 MIN	0.902	0.037	32.627	98.179
SA4- 45 MIN	0.91	0.037	32.921	99.253
SA5- 45 MIN	0.911	0.037	32.957	99.794
SA6- 45 MIN	0.91	0.037	32.921	99.549
SA1- 60 MIN	0.916	0.038	32.953	99.445
SA2- 60 MIN	0.917	0.038	32.989	99.949
SA3- 60 MIN	0.922	0.038	33.172	99.819
SA4- 60 MIN	0.916	0.038	32.953	99.350
SA5- 60 MIN	0.917	0.038	32.989	99.891
SA6- 60 MIN	0.916	0.038	32.953	99.646

Ps. HCl: Pseudoephedrine hydrochloride, nm: Nanometer, conc.: Concentration, mg/ml: Milligram/milliliter, Q: quantity.

Appendix G: Orphenadrine citrate dissolution

The pellet weight in each chamber of the USP apparatus and the Orphenadrine citrate quantity in each is depicted in (Table 37)

Table 37: Orphenadrine citrate sample weight used for dissolution

Sample #	Pellets weight (mg)	API quantity
1.00	100.52	32.27
2.00	100.65	32.31
3.00	100.48	32.25
4.00	100.59	32.29
5.00	100.50	32.26
6.00	103.57	33.25

Mg: Milligram, API: Active pharmaceutical ingredient

Dissolution of orphenadrine citrate from the pellet formulation in water was calculated and (Table 38) represent the quantity of drug released at each time point

Table 38: Orphenadrine citrate dissolution calculations

Sample (Orph. citr.)	Absorbance (nm)	C1 (mg/ml) y = 43.388x + 0.0059	Q (mg) (C1) *900	C2 (mg/ml) time 10 to 60 C2*25	C2 time 10 to 60/4	Q (mg) C2*900	% Release (Q/API quantity)
SA1- 5 MIN	0.935	0.0214	19.272				59.728
SA2- 5 MIN	1.027	0.0235	21.181				65.557
SA3- 5 MIN	0.909	0.0208	18.733				58.079
SA4- 5 MIN	0.986	0.0226	20.330				62.962
SA5- 5 MIN	0.93	0.0213	19.169				59.418
SA6- 5 MIN	0.981	0.0225	20.227				60.839
SA1-10 MIN	0.22	0.0049		0.123	0.031	27.603	85.544
SA2-10 MIN	0.223	0.0050		0.125	0.031	27.989	86.631
SA3-10 MIN	0.221	0.0050		0.124	0.031	27.732	85.978
SA4-10 MIN	0.223	0.0050		0.125	0.031	27.989	86.682
SA5-10 MIN	0.22	0.0049		0.123	0.031	27.603	85.561

SA6-10 MIN	0.223	0.0050		0.125	0.031	27.989	84.188
SA1-20 MIN	0.236	0.0053		0.133	0.033	29.334	90.910
SA2-20 MIN	0.236	0.0053		0.133	0.033	29.334	90.792
SA3-20 MIN	0.233	0.0052		0.131	0.033	28.951	89.760
SA4-20 MIN	0.239	0.0054		0.134	0.034	29.716	92.031
SA5-20 MIN	0.233	0.0052		0.131	0.033	28.951	89.742
SA6-20 MIN	0.239	0.0054		0.134	0.034	29.716	89.383
SA1-30 MIN	0.247	0.0056		0.139	0.035	30.389	94.179
SA2-30 MIN	0.25	0.0056		0.141	0.035	30.767	95.228
SA3-30 MIN	0.247	0.0056		0.139	0.035	30.389	94.217
SA4-30 MIN	0.25	0.0056		0.141	0.035	30.767	95.285
SA5-30 MIN	0.247	0.0056		0.139	0.035	30.389	94.198
SA6-30 MIN	0.25	0.0056		0.141	0.035	30.767	92.543
SA1-45 MIN	0.251	0.0056		0.141	0.035	30.540	94.647
SA2-45 MIN	0.256	0.0058		0.144	0.036	31.163	96.453
SA3-45 MIN	0.251	0.0056		0.141	0.035	30.540	94.685
SA4-45 MIN	0.254	0.0057		0.143	0.036	30.914	95.739
SA5-45 MIN	0.25	0.0056		0.141	0.035	30.415	94.280
SA6-45 MIN	0.256	0.0058		0.144	0.036	31.163	93.734
SA1-60 MIN	0.261	0.0059		0.147	0.037	31.419	97.370
SA2-60 MIN	0.264	0.0059		0.149	0.037	31.788	98.388
SA3-60 MIN	0.261	0.0059		0.147	0.037	31.419	97.409
SA4 60 MIN	0.263	0.0059		0.148	0.037	31.665	98.065
SA5-60 MIN	0.26	0.0059		0.146	0.037	31.295	97.008
SA6-60 MIN	0.264	0.0059		0.149	0.037	31.788	95.614

Orph. Citr: orphenadrine citrate, nm: Nanometer, conc.: Concentration, mg/ml: Milligram/milliliter, Q: quantity.