Effect of Microcrystalline Cellulose in the Extrusion-Spheronisation Process of Microparticulate-Making Technology: A Systematic Review

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Abstract

Effect of Microcrystalline Cellulose in the Extrusion-Spheronisation Process of Microparticulate-Making Technology: A Systematic Review.Multiparticulate consists of several preparations including mini-tablets, powders and pellets. In this review, the aim is to identify the characteristics of microparticulates, especially pellet preparations based on Microcrystalline Cellulose (MCC) using extrusion-spheronisation. Extrusion-spheronisation is the most widely used technique of making pellets involving dry mixing, wet granulation, extrusion, and spheronisation. MCC is the most commonly used additive in the manufacture of pellets in extrusion-spheronisation because it can create pellets with low friability, high porosity, and a smooth surface. However, the shortcoming of MCC-based pellets is the dissolution process is very slow requiring combination with other excipients such as polysorbate 80 and PEG 400. In addition, different treatments on other pellets require the use of different granulation liquids so that they play a role in dissolution. In addition, pellets with a drying process using hot air have smaller sizes compared to those using freeze drying.

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INTRODUCTION

The rapid advancement of technology in the pharmaceutical sector has made way for innovations in the development of drugs and their available forms. The pharmaceutical industry has been focusing on optimizing a drug delivery system that is able to streamline active substances to improve drug performance and provide a therapeutic effect [1]. Multiparticulate drug delivery systems consist of various dosage forms including mini-tablets, pellets, and powders, among others [2].

Mini-tablets are a solid pharmaceutical preparation with a size of 1.0 mm. According to the World Health Organization (WHO), mini-tablets are preparations that have a size of not more than 4.0 mm. Mini-tablets are the right choice for paediatrics and geriatrics today [3]. Pellets are small, free-flowing solid units that are spherical or semi-spherical, have a size of about 0.5 mm - 1.5 mm, and are usually intended for oral administration [4] and are usually placed in hard gelatine capsules, but can also be compressed into tablets [5]. Powder is a powdered dry mixture of medicinal substances or chemical substances, intended for oral use or external use. Due to its large surface area, powder is more easily dispersed and more soluble than the compacted dosage form [6].

A multiparticulate system is a preparation consisting of many units. Multiparticulate formulas can contain a single drug or various drug combinations ranging from particles that are orally soluble, with immediate release or multiple modified releases. The widely marketed multiparticulate products consist of balls coated with immediate release. Coating aims to protect or cover the taste [7].

Multiparticulate, especially for pellet preparations, has been proven to be superior to tablet dosage forms in terms of loose preparations [2]. Pellet preparations have technical and pharmacological advantages such as fast absorption, high bioavailability, good flow rates, and easy coating [8]. The purpose of pelletisation is to produce spherical particles with a narrow size distribution and acceptable mechanical properties for the desired release patterns. Among various techniques of

making pellets, extrusion-spheronisation is the technique most widely used. This technique involves two processes: extrusion and spheronisation. Extrusion is the process of manufacturing a wet mass consisting of active and excipient ingredients (fillers and binders) or without active ingredients which will then be formed into long, thin rods called extrudates. Spheronisation is the process wherein the extrudates obtained from the first stage will be spheronised to produce uniform pellets [9].

Extrusion-spheronisation is a technique of producing pellets or microspheres. There are many factors that affect the production of pellets with this technique, two of which are related to the formulation and the process [10]. In the case of formulation, it is important that all the materials selected are plastic and deformable during the required processing time, and the materials are less sticky during processing. The principle of the spheronisation process (Figure 1) is that wet materials with plastic properties are transferred to a spherical shape [11].

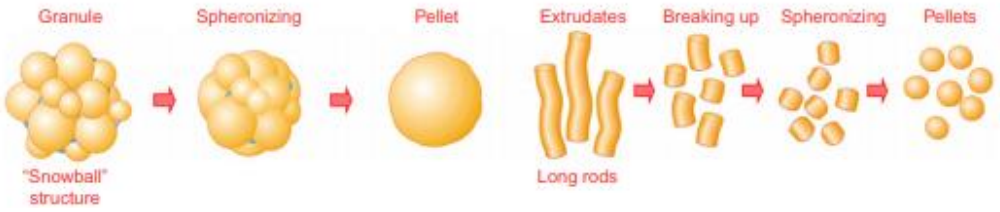

Figure 1. The basic principle of spheronisation with two applications [11].

The extrusion-spheronisation process (Figure 2) involves several steps including dry mixing, wet granulation, extrusion, spheronisation, drying, and optional screening [5]. The main advantage of pellets made by extrusion-spheronisation is their ability to combine high levels of active ingredients without producing too large particles [12].

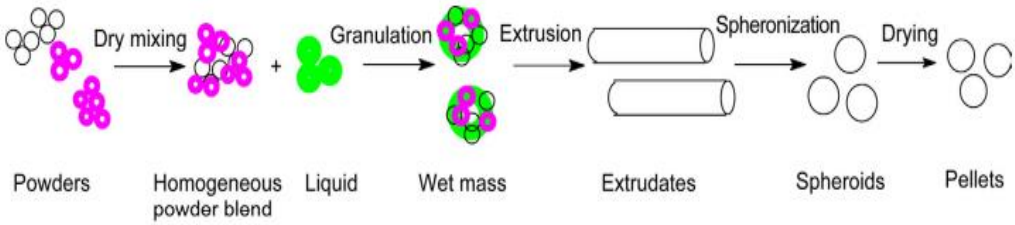

Figure 2. Sequential extrusion process of spheronisation [5].

Extrusion-spheronisation is more intensive than the other granulation processes; thus, it should be carefully considered if a granulation process is not suitable for a particular formulation. Extrusion-spheronisation can be used to increase bulk density, improve flow properties, and reduce dust production. However, determining the composition of the wet mass is highly important in influencing the properties of the resulting particles. During the granulation process, the wet mass produced should be plastic, change shape during the extrusion process, and break down to form uniformly sized cylindrical particles that easily change shape into pellet particles [13]. Microcrystalline Cellulose (MCC) is chosen in the formation of pellets using the spheronisation method because it has plasticity in forming wet mass [14].

Cellulose is an abundant biopolymer natural material derived from biomass. It can be extracted from natural fibres such as rosella, cotton, wood, hemp, palm oil, and coir. MCC has been recognized as partially hydrolysed and depolymerised cellulose consisting of amorphous irregularities [15]. The function of Microcrystalline Cellulose largely depends on its physical properties, which in turn will affect the control of the process and the quality of the final product [16].

EXPERIMENITAL

The process of reviewing this article was carried out by collecting information from published national and international scientific journals using search engines including Scopus, Science Direct,

and Google Scholar. The keywords used to search the journals in these sites were extrusion/spheronisation, formulations, Microcrystalline Cellulose, pellets, and technology. There were 14 international journals and one national journal found related to these keywords.

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RESULT AND DISCUSSION

Effect of spheronisation time on the shape of the pellets produced

Extrusion-spheronisation is the most popular technique in the pellet-making process in which the resulting pellets can have near perfect shape. Figure 3 shows the pellets yielded in the spheronisation process of the extrudate mass with the same diameter showing an almost spherical shape [17].

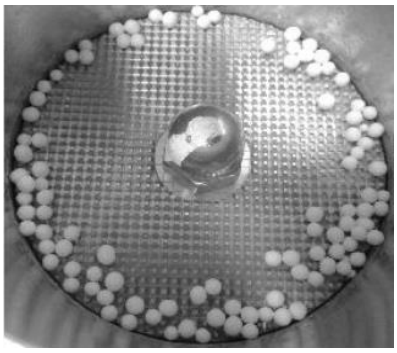

Figure 3. The pellets in the spheroniser after 8 minutes of rotation [17].

In this case, spheronisation time greatly affects the amount of pellet rendement produced. The longer the time, the larger spheronisation energy produced to break down the extrudate, causing the resulting pellet rendement to be smaller; and the more energy produced to break down the extrudate, the more extrudate will be split into fine powders [18].

The effect of the drying process on the physical properties of the pellets and the size of the pellets produced

As seen in Figure 4, MCC can be formed into pellets with the help of water as the granulation liquid. However, there are differences in the two images due to different conditions. Figure 4(a) shows that there was a colour change in the pellets that were dried in an oven at 40°C for 15 minutes, whereas Figure 4(b) shows the pellets did not have a change in their aesthetic properties when they were dried in the microwave. This occurs because microwaves use microwave radiation for drying and the duration of exposure is lower, making the drying of the pellets fast and does not affect the physicochemical properties of the pellets [12].

Figure 4. Drug-laden MCC pellets using water as the granulating material and drying in an oven at 40°C for 15 minutes (a) drying in a microwave for 3 minutes (b) [12].

Table 1 describes the size distribution of the pellets dried using three drying techniques. The sieving analysis show that the size distribution is narrow for most of the formulations. The drying conditions affect the average size of the pellets. Size fraction is typically 1.18 - 1.40 mm for hot air and microwave dried pellets. On the other hand, the pellets dried with freeze dryer obtain the average size

of 1.40 - 1.70 mm. The mean size of the pellets dried using hot air is significantly smaller than those dried using freeze dryer ($p < 0.05$), indicating that shrinkage occurred in the drying process using high temperatures [19].

Table 1. Effects of three drying techniques on particle size distribution in MCC-based pellets; with the composition of paracetamol pellets (6.7% w/w), MCC (66.7% w/w), and Dicalcium Phosphate (26.6% w/w) [19]

Size Fraction (mm)	Weight retained per fraction (%, w/w)		
	Hot Air Oven	Microwave Oven	Freeze Dryer
> 1.70	0.9	3.7	9.8
1.40–1.70	5.5	10.8	69.6
1.18–1.40	57.1	61.7	12.4
1.00–1.18	23.3	16.5	4.1
0.85–1.00	8.4	6.8	1.8
0.60–0.85	4.6	0.4	1.0
<0.60	0.2	0.1	1.3

Effects of Microcrystalline Cellulose on physical properties, disintegration time and drug release

Figure 5 displays the pellet disintegration process tested at room temperature in static conditions. It can be seen that the MCCTP pellets (containing polysorbate 80 and PEG 400) started to split into two parts at 60 seconds and the MCCTPC2 pellets (containing polysorbate 80, PEG 400, and Crosscarmelosa Sodium) started to break after 4 seconds into many fragments. However, the MCC-based pellets were not completely destroyed until 150th second as shown in Figure 5.

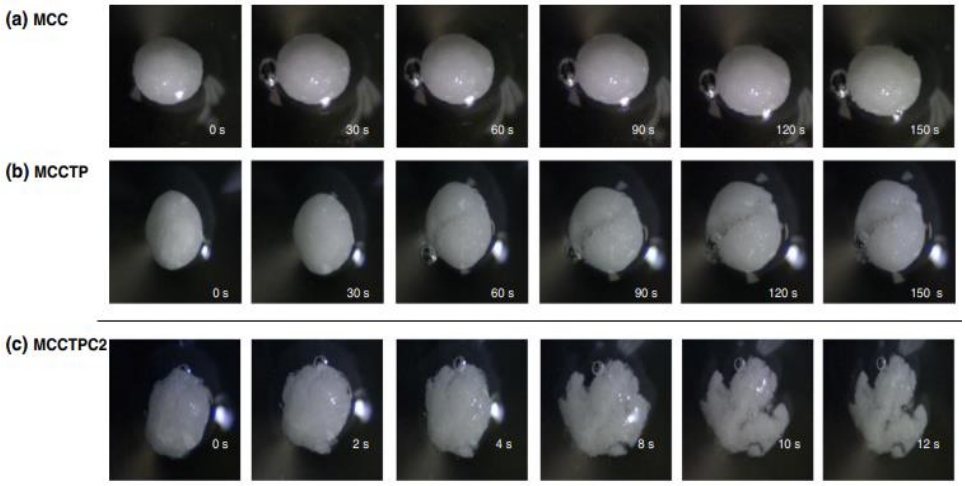

Figure 5. Pellet images taken from MCC-based pellet disintegration video; (a) MCC; (b) MCCTP; and (c) MCCTPC2 [20].

Other observations on the surface and cross-section of the pellets were carried out by using SEM. As shown in Figure 6, MCC pellets have a smooth surface with an internal structure that has a cavity inside. This is perhaps influenced by the rotation and friction forces involved in the spheronisation process. A more porous structure can be seen in Figure 6b-d with the pellets containing polysorbate 80 or PEG 400 or a combination of these, and a larger cavity can be found in Figure 6e with the pellets containing Crosscarmelosa Sodium. These results are consistent with the mechanical findings which show that pellets containing polysorbate 80, PEG 400 and Crosscarmelosa Sodium have lower crushing strength and higher porosity than MCC pellets [20].

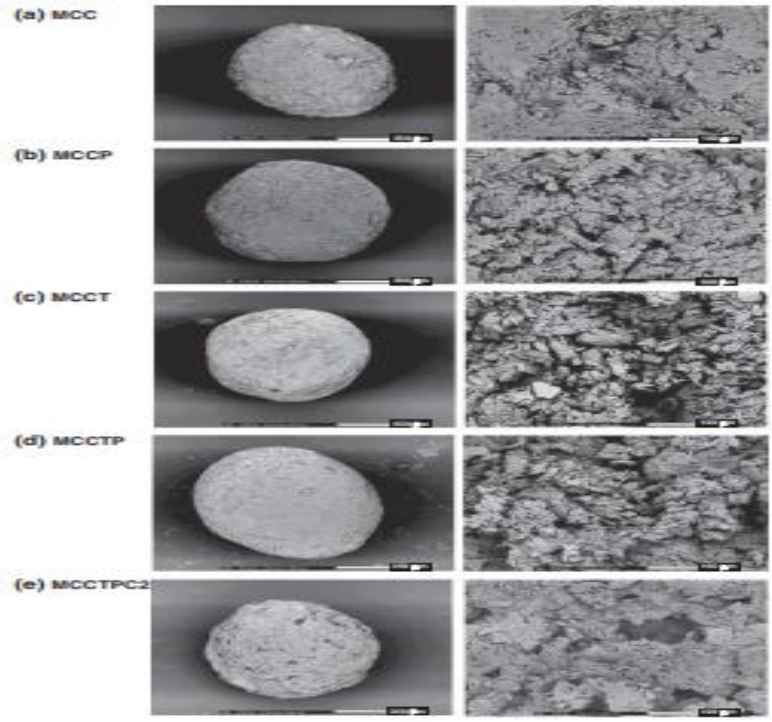

Figure 6. Electron micrograph images of IMC pellets; (1) external structure (30x) and (2) internal structure (100×) [20].

The dissolution profile of Indomethacin MCC-based pellets shown in Figure 7 reveals that the pellets had a slow release (37% of the drug was dissolved within 120 minutes) because they were not destroyed. This is due to the shrinkage of MCC during drying, resulting in less porous pellets. The addition of polysorbate 80 and PEG 400 to the formula indicates an increase in drug release. In Figure 7, the drug added with polysorbate 80 shows a greater release compared to that with PEG 400. PEG 400 is a pore-forming agent which causes a spongy matrix due to recrystallization during the drying process, and thus, the pellets produced are stiffer than MCC pellets. On the contrary, polysorbate 80 is a non-ionic surfactant that can dissolve homogeneously with medicinal powders or excipients. The combination of polysorbate 80 and PEG 400 significantly increases drug dissolution from the pellets, and this can provide a hydrophilic environment to increase drug solubility resulting in faster drug dissolution [20].

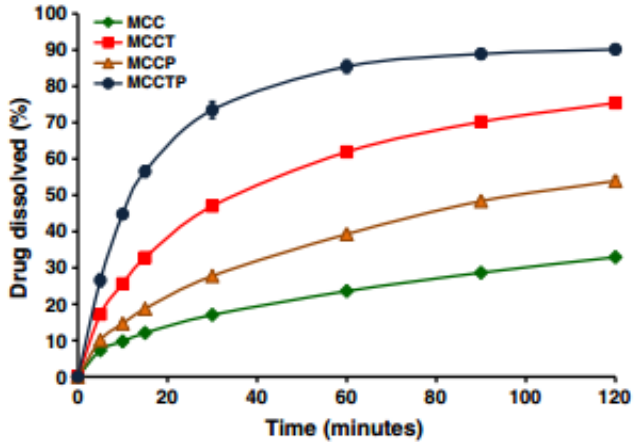

Figure 7. Indomethacin dissolution profile from MCC-based pellets containing PEG 400 and polysorbate 80 [20].

Similarly, the drug dissolution profile shown in Figure 8 shows that MCC- based pellets did not affect drug release rates. The addition of Etylcellulose to the pellets was also insignificant because despite its hydrophobic nature, Etylcellulose was unable to form a strong matrix in the pellet structure.

Therefore, MCC-based pellets in Theopilin drug pellets require the use of granulation liquid using Surelease which plays an important role in the drug release profile [21].

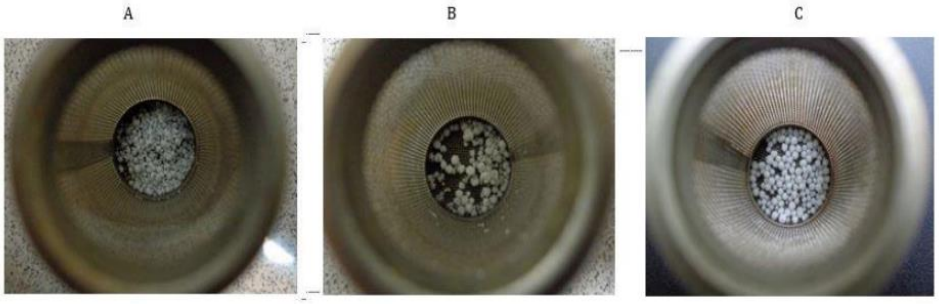

Figure 8. Theopilin pellets after dissolution test [21].

CONCLUSION

The extrusion-spheronisation process has shown promising results in the pellet formation with Microcrystaline Cellulose (MCC). This journal review concludes that extrusion-spheronisation is the simplest method used in the microparticulate formation process, especially in the pellet preparation with the help of MCC as a pellet base. This base contributes to the characteristics of the pellet formation with satisfactory roundness, low friability, high porosity, and smooth surface. The pellets have unique properties and good bonding that can create compactness in the wet mass. The drying process of the wet mass using several drying techniques determines the size of the pellets produced. The drying process using hot air significantly produces a smaller pellet size compared to using freeze dryer. MCC-based pellets have higher resistance, so they are not easily destroyed, whereas MCC-based pellets with a low level of brittleness cause slower dissolution process. Thus, to increase the dissolution of MCC-based pellet drugs, the combination with other materials such as polysorbate 80 and PEG 400 is necessary.

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