The Effect of Particle Size on the Physical Characteristics and Drug-release Behavior of Mini-tablets

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Abstract

This study aimed to investigate the influence of particle size of the excipients on the behavior of mini-tablets in terms of physical characteristics and drug release profiles. Material and methods: All of the mini-tablets based on HPMC, PEG 6K and PEO 8M PVP produced high quality mini-tablets from both sieve fractions while 90F was very fragile. Results: Crushing strength values were the most pronounced difference between the mini-tablets from all formulations. The PEO 8M-based mini-tablets showed the highest values and deformation behavior instead of fracture. Water absorption and drug release profiles also showed intriguing and different results between the various formulations. Conclusion: The results suggested that even though different particle size has limited effect on the physical characteristic of the product, it may have a significant effect on its drug dissolution profile.

Keywords: Drug release profile, Mini-tablets, Particle size, Physical characterization

Introduction

Conventional tablets usually are round in shape with a minimum diameter of 7 mm. On the other hand, mini-tablets are smaller, with a diameter between 2 and 3 mm or less [1]. Mini-tablets can either be filled into hard-shell capsules or compacted into larger tablets for controlled release formulation [2]. The process of manufacturing mini-tablets is similar to those of regular-sized tablets. However, mini-tablets manufacturing requires special attention in certain areas, such as the particle size distribution of the powders or granules [3].

The particle size of the powders or granules needs to be controlled during the manufacturing process. If the particle size is too large, only several particles can be fitted in the die. However, if the particles size is too fine, there is a possibility for the powder to pass through the gap between the die and the punch. Both scenarios will likely affect the content uniformity of the excipients and active ingredients, affecting the weight and active ingredients dosage of the mini-tablets. Since smaller particle size has larger total surface area, alteration of the particle size distribution may also affect the drug release profile of the mini-tablets.

This study evaluated the effect of particle size on the physical characteristics and drug-release behavior of the mini-tablets. Chloramphenicol, a broad-spectrum antibiotic for bacterial infection treatment, was used as the model drug. The formulations used in this study were prepared using direct compression to ensure that the investigation was primarily focused on particle size distribution only.

Materials and methods

Materials

Hydroxypropyl methylcellulose K4M (HPMC) was purchased from The DOW Chemical Company, USA. Polyethylene glycol 6000 (PEG 6K) was purchased from Clariant GmbH, Germany. Polyvinylpyrrolidone 90F (Kollidon 90FTM) (PVP 90F) was provided by BASF The Chemical Company, Germany. Polyethylene oxide 8,000,000 (PEO 8M), chloramphenicol, calcium chloride, and sodium bicarbonate were obtained from Sigma Aldrich, Germany. Sodium stearyl fumarate (SSF) was obtained

from Tokyo Chemical Industry, Japan. Sodium chloride was obtained from Fluka Chemie GmbH, Germany.

Methods

Manufacturing process of the mini-tablets

All the mini-tablets were prepared with 5 % w/w chloramphenicol, 2 % w/w SSF and 93 % w/w polymer. The polymers employed in this study were HPMC, PEG 6K, PEO 8M and PVP 90F. Two sieve fractions were evaluated for each polymer, which were 125 to 180 and 180 to 250 μ m. The drug and polymer were mixed using a Turbula mixer for 10 min. SSF was added and mixed for another 5 min. Mini-tablets were compressed with a rotary tablet press (Riva, Argentina) equipped with 2 mm normal concave plain punches at a compression force of 1.8 ± 0.2 kN [4]. Only 1 set of tooling was used during the process. Approximately, 100 mini-tablets per batch was manufactured for each formulation.



Figure 1 Manufactured mini-tablets.

Physical characterization of the mini-tablets

Weight uniformity

The weight uniformity of the mini-tablets was evaluated following the British Pharmacopoeia [5] method. Twenty tablets were selected randomly from each formulation and weighed individually. The mean weight and standard deviation were calculated.

Measurement of mini-tablet dimensions

The thickness of 10 random tablets from each formulation was measured with a digital caliper (Mitotoyo, Japan). The diameter was assumed to be constant at 2 mm, based on the diameter of the punches.

Friability

The tablets' friability was determined by weighing 10 tablets as a unit, followed by placing the tablets in a friability tester drum (Copley Scientific, UK). The drum was configured to rotate for 100 revolutions at the speed of 25 rpm. The tablets were dedusted and re-weighted to calculate the percentage of friability using following equation:

$$F(\%) = \left(\frac{P - P'}{P}\right) \times 100 \tag{1}$$

where P is the initial weight of the tablets, and P' is the final weight of the tablets.

Crushing strength

Ten random tablets were assessed with a TA.TX2 texture analyer (Stable Microsystems Ltd, UK) according to the method by El-Gawad [6]. The mini-tablets placed on the fixed platform were crushed with an 11 mm diameter Perspex cylinder probe that was attached to the texture analyzer. This study's instrument parameters were: 1 mm/s pre-test speed, 0.1 mm/s test speed, 1 mm/s post-test speed, 1 mm compression distance and 0.05 N trigger force. The force required to crush the tablets were recorded.

Moisture uptake

The mini-tablets' moisture uptake profile was monitored with dynamic vapor sorption (DVS) (Surface Measurement Systems, UK) at a fixed humidity level of 95 ± 1 % RH for over 24 h. Three random tablets were tested for each formulation.

Drug release studies

A modified flow-through dissolution apparatus with a 200 μ L chamber was used to assess the minitablets' drug release profile. Simulated tear fluid (STF) with a pH of 7.4 was prepared with 0.2 % w/w sodium bicarbonate, 0.008 % w/w calcium chloride and 0.67 % w/w sodium chloride [7] and used as dissolution medium. The flow rate of the dissolution medium was fixed at 50 μ L/min. The samples were collected hourly for 9 h. Drug concentration in the samples was quantified spectrophotometrically at 278 nm. Three replicates were performed for each formulation.

Statistical analysis

The data were analyzed with the Statistical Package for Social Sciences (SPSS) and Microsoft Excel. Analysis of variance (ANOVA) was applied to determine any significant (p < 0.05) differences in the mini-tablets' physical parameters.

Results and discussion

Physical characterization of the mini-tablets

Table 1 summarizes the physical characterization data for the mini-tablets, except for vapor sorption. Each of the characterization studies is discussed in detail in the following sections.

Polymer	Sieve Fraction (µm)	Weight (mg) (n = 20)	Thickness (mm) (n = 10)	Friability (%) (n = 3)	Crushing strength (N) (n = 10)
HPMC	125 - 180	6.26 ± 0.34	1.89 ± 0.03	0.22 ± 0.01	12.43 ± 1.74
HPMC	180 - 250	6.20 ± 0.21	1.91 ± 0.04	0.16 ± 0.06	17.11 ± 2.55
PEG 6K	125 - 180	5.50 ± 0.35	1.58 ± 0.04	0.48 ± 0.04	8.24 ± 1.29
PEG 6K	180 - 250	9.75 ± 0.29	2.79 ± 0.04	0.34 ± 0.07	12.10 ± 1.38
PEO 8M	125 - 180	6.97 ± 0.08	2.22 ± 0.01	0.03 ± 0.01	43.18 ± 1.44
PEO 8M	180 - 250	7.40 ± 0.09	2.33 ± 0.02	0.05 ± 0.02	40.07 ± 2.06
PVP 90F	125 - 180	7.84 ± 0.07	2.43 ± 0.01	1.44 ± 0.25	5.84 ± 0.59
PVP 90F	180 - 250	7.43 ± 0.10	2.34 ± 0.02	9.92 ± 0.69	5.64 ± 0.99

Table 1 Summary of the physical characterization of mini-tablets (mean \pm SD).

Weight uniformity

The weight of all the mini-tablets was within the specification of British Pharmacopoeia [5]. Each polymer displayed a similar weight between the sieve fraction except for PEG 6K, where the larger particle size powder showed higher weight.

Thickness

The range of measured thickness values was between 1.89 ± 0.03 and 2.79 ± 0.04 mm. All batches displayed an acceptable level of variation, which was supported by the relative standard deviation (RSD) values. It could be suggested that all the mini-tablets from the same batch had a similar thickness. A statistically significant difference (p < 0.05) was observed between the 2 sieve fractions of PEO 8M and PVP 90F mini-tablets. PEG 6K mini-tablets showed a significant difference where the larger sieve fraction had thicker tablets than the smaller sieve fraction. There was no significant difference between the thickness of the 2 sieve fractions of HPMC mini-tablets.

Crushing strength

The crushing strength results displayed a wide range of values between 5.64 ± 0.99 and 43.18 ± 1.44 N, as shown in **Table 1**. PVP 90F mini-tablets had the lowest crushing strength, followed by PEG 6K, HPMC and PEO 8M mini-tablets for both sieve fractions. There is a lack of crushing strength specification in the British Pharmacopoeia. However, based on previous studies on mini-tablets, the common value of hardness is in the range of 0.67 to 18.64 N [8,9]. Crushing strength value showed a correlation with the disintegration and dissolution profiles of the tablets, where higher crushing strength have longer disintegration and dissolution time [10].

PEO 8M mini-tablets from both sieve fractions had the highest crushing strength. These tablets displayed distinct behavior than the rest of the mini-tablets. Instead of breaking, the PEO 8M mini-tablets were just deformed. The recorded endpoint was the force to compress the tablets at the end of the probe's fixed-distance travel. Hence, the PEO mini-tablets measurements should not be over-interpreted even though they were consistent with low RSD values.

The rest of the mini-tablets exhibited typical breaking behavior. No significant difference (p > 0.05) was observed in the crushing strength of both PVP 90F mini-tablets sieve fractions. However, HPMC and PEG 6K mini-tablets showed significant differences (p < 0.01), with the larger sieve displaying greater crushing strength. This result is counter-intuitive since theoretically, smaller particle size fraction would have increased binding and greater resistance to crushing due to increased contact between the particles. These batches had higher RSD values, which were beyond 10 %. Even though a standard is absent in the British Pharmacopoeia, the crushing strength should be kept consistent since it may affect the tablets' dissolution behavior.

Friability

According to the British Pharmacopoeia [5], the percentage of weight loss should not exceed 1.0%. All the mini-tablets, except for PVP 90F mini-tablets for both sieve fractions, passed the friability test. The losses in percentage of smaller and larger sieve fractions of PVP 90F were 1.44 ± 0.25 and 9.92 ± 0.69 %, respectively.

These results were expected since, theoretically, higher crushing strength comes with lower friability. Friability test is essential since it mimics the external forces that the tablets will experience during the handling and transporting processes of the product from the manufacturing process to administration by the patient. The drug dosage can be reduced proportionally with the weight of the tablet. Therefore, the tablet's therapeutic outcome may be compromised with its weight loss [11].

Moisture uptake

Figure 1 shows the moisture uptake of the mini-tablets over 24 h. PEO 8M ($125 - 150 \mu m$) minitablets showed the most significant changes in their weight after 24 h, while the lowest weight gain was for PVP 90F ($180 - 250 \mu m$) mini-tablets, at approximately 130 and 40 % weight increment from the initial weight, respectively. PEG 6K and PEO 8M mini-tablets for both sieve fractions were completely dissolved at the end of the study. HPMC and PVP 90F mini-tablets for both sieve fractions absorbed water and showed swelling symptoms.



Figure 2 Percentage of weight changes from moisture uptake of mini-tablets.

HPMC and PVP 90F formulations displayed similar weight changes between the 2 size fractions, with weight increments between 40 and 50 %. The weight drastically increased within the first h and plateaued after 3 h. PEG 6K and PEO 8M formulations showed gradual weight changes with huge weight increments, where smaller sieve fraction mini-tablets absorbed more moisture than their counterparts. The smaller sieve fractions absorbed approximately 130 % moisture, while the larger sieve fraction absorbed roughly 100 % moisture compared to their initial weights. The larger sieve fraction approached a plateau at the end of the 24 h experiment, while the smaller sieve fraction continued to acquire moisture until the point of experiment termination.

Drug release studies

A modified flow-through dissolution apparatus was used for the dissolution study. This setup was based on a study by Brown *et al.* [12] on dissolution methodology for granules. Since the size of the minitablets and granules were roughly similar, this method was applicable for the minitablets. The minitablets were inserted into a 200 μ L chamber and flowed with STF at a rate of 50 μ L/min. The samples were collected hourly for 9 h and spectrophotometrically quantified at 278 nm. **Figure 2** shows the release profiles of all mini-tablets.



Figure 3 Drug release profiles of mini-tablets (mean \pm SD, n = 3).

All tablets were completely dissolved at the end of the dissolution experiment. Chloramphenicol from PVP 90F and PEG 6K mini-tablets of both sieve fractions was completely released. More than 80 % of the chloramphenicol in HPMC mini-tablets (both sieve fractions) and PEO 8M (180 - 250 μ m sieve fraction) mini-tablets were released within 9 h timepoint. Only 60 % of the chloramphenicol in PEO 8M (125 - 180 μ m sieve fraction) mini-tablets was released at the end of the experiment. PEO 8M formulation of both sieve fractions had almost linear release profiles compared to the rest of the formulations in the graph.

Conclusions

This study investigated the effect of particle size on the physical behavior and drug release characteristics of mini-tablets. All formulations produced high-quality mini-tablets, except for PVP 90F, which displayed a characteristic of high friability. PEG 6K and PEO 8M mini-tablets of the larger sieve fraction variation absorbed less moisture with faster release of drugs than their counterparts. Meanwhile, HPMC and PVP 90F mini-tablets of both sieve fractions showed similar pattern in term of moisture uptake and drug release profiles. PEO 8M mini-tablets of both sieve fractions displayed almost linear release profiles with the highest crushing strength than the rest of the formulations. In conclusion, the polymer's particle size in mini-tablets had a little bearing on the products' physical characteristics, although it could significantly affect the product's dissolution profile.

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