The effect of disintegrants on the physical properties of a cocoa butter based fast melt tablet developed by a fusion moulding method.

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Technical Note

ABSTRACT

Oral dispersible tablets (ODTs) generally have high porosity and disintegrate using mechanisms such as wicking of water by the disintegrant and the dissolving of water soluble excipients. An alternative to ODT is a fast melting tablet (FMT) that can disintegrate within 3 minutes and which does not have the friability, packaging or cost issues associated with ODTs. The development of fusion molded tablets using cocoa butter as a base combined with a suitable disintegrant has not been previously explored. This study was designed to formulate FMTs using cocoa butter as a base and study the effect of the addition of disintegrants on the resulting FMTs. Microcrystalline cellulose, starch and sodium starch glycolate were incorporated at various amounts and their effect on FMT physical properties was compared. The physical characterization tests performed were hardness, weight variation, thickness, friability and disintegration time. Formulation F7 containing 30% MCC showed the greatest hardness (1.30 ± 0.53 kg), lowest friability (0.16%) and shortest disintegration time (103.00 ± 4.16 seconds). These properties did not change when stored for 9 months at 30 ± 1°C.

KEY WORDS: Cocoa butter, fast melt tablet, microcrystalline cellulose, MCC, sodium starch glycolate, SSG, corn starch, oral dosage forms, orally disintegrated tablet, ODT

INTRODUCTION

Oral solid dosage forms remain the most common and accessible dosage forms utilized. However, there are patients, including children and the elderly that may find it difficult to swallow conventional tablets and capsules. Appropriate dosage form selection plays a major role and has an impact on patient safety, therapeutic outcomes and patient compliance (1). In recent years there has been increasing interest in orally disintegrating tablets (ODT) as a preferable alternative to conventional solid oral dosage forms.

ODTs are also known as fast dissolving, rapidly disintegrating, quick-dissolving, crunch-melt, bite-dispersible, mouth-dissolve, and orodispersible tablets (2). The British Pharmacopoeia defines ODTs as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" and their disintegration time is within 3 minutes (3). Rapid disintegration of the ODTs is beneficial to patients who have difficulty in swallowing medication. Badgujar *et. al.,* stated that when the ODTs come into

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contact with saliva, they will disintegrate immediately and produce a suspension that can be easily swallowed by the patient (4). The active ingredients in the solution are more rapidly absorbed through the pre-gastric route from the mouth, pharynx, esophagus and through gastrointestinal epithelium to produce the desired effect. Additionally, Thakur *et. al.*, have stated that rapid disintegration results in quick dissolution and enhance the absorption of the drugs thus resulting in rapid onset of action (5).

However, formulating an ODT is not a trivial exercise. An ODT formulation must consider many factors such as taste, texture, smell and after-taste to ensure patient compliance (6). ODT formulations may incorporate fillers, disintegrants, lubricants, glidants, sweeteners and flavors in addition to the Active Pharmaceutical Ingredient (API)I (7). Superdisintegrants play an important role in the formulation of ODTs providing faster disintegration times (8).

ODTs can be manufactured by various conventional manufacturing methods including direct compression. The addition of a suitable amount of superdisintegrant produces ODTs with fast disintegration and good stability (9). Freeze drying has also been used to produce ODTs. This process involves the removal of solvents from a frozen drug solution or suspension (10). Freeze-drying produces ODTs with porous structure ensuring rapid penetration of the saliva into the pores followed by rapid tablet disintegration. However, lyophilized ODTs are very friable, highly sensitive to moisture and have weak mechanical strength. They require special blister packaging ("peel-off" blisters) (11). Tablet molding produces ODTs that are highly porous in structure, resulting in a high rate of disintegration and dissolution. The API is moistened, dissolved, or dispersed in a solvent. The moist mixture is then molded into tablets by applying lower pressure in a compression molding. The powder mixture may be sieved prior to the preparation to increase the dissolution rate (9). The tablets produced generally have low mechanical strength (12).

There are also other methods published to produce ODTs such as phase transition, spray drying, sublimation and cotton candy base (9-12). Most of the published methods rely on three disintegration mechanisms namely wicking of water into the tablet matrix (direct compression, wet granulation), dissolution of the water soluble ingredient (tablet molding), and porous structure of the ODT (spray drying, lyophilization, cotton candy base). There is thus a valid need to search for alternative methods to manufacture ODTs which would not be as friable, would not require specialized packaging or would be as costly.

Theobroma oil or cocoa butter is a yellowish white solid, with an odor resembling that of cocoa. It tastes bland and agreeable and is generally extracted by expression from the seed of the cocoa bean. It has excellent emollient properties and is used to soften and protect chapped hands and lips. It has also greasing and lubricating properties. Cocoa butter is thus a good excipient for feel and firmness in lip balms, softening hand creams, moisturizing soaps, skin emollient creams. It is used as an excipient in ointments and for coating tablets and suppository preparations. Cocoa butter is a key ingredient for producing chocolate (13). It is brittle at temperatures below 25°C, and melts in the mouth at a temperature of 34°C. It also contains fat soluble antioxidants such as vitamin E in the form of β-tocopherol, α-tocopherol and γ-tocopherol. Cocoa butter can crystallize into several polymorphic forms, having α, γ, β' and β crystals, with melting points of 17, 23, 26, and 35-37°C respectively (14).

The objective of this study was to explore a new FMT manufacturing method using cocoa butter as base. Three types of disintegrants were added at various concentrations to investigate their effect on the physical properties of the FMT. No API was incorporated into the FMT.

MATERIALS AND METHODS

Materials

Food grade cocoa butter was obtained from Personal Formula Resource (Malaysia) corn starch (unknown viscosity and particle size) and Sodium Starch Glycolate Type A (SSG) were purchased from Sigma

Aldrich (Malaysia), Microcrystalline cellulose (MCC) Avicel® PH 101 was purchased from R&M Chemical (Malaysia).

Melting point determination by Differential Scanning Calorimetry

A Perkin-Elmer Pyris 6 System DSC (Perkin-Elmer, USA) was used for melting point determination. 5 mg cocoa butter, was weighed in an aluminum pan and crimped. The heating rate was 10°C/min from 0 to 100°C under nitrogen flow (20 cm3/min). An empty aluminum pan was used as a reference.

Preparation of fusion moulded tablets containing cocoa butter

Fusion molded tablets containing cocoa butter were prepared using the molding method. The various ratios of the cocoa butter based FMT formulations are presented in Table 1. The percentage of superdisintegrants used in the formulations were 10%, 20% and 30%. The superdisintegrants used in the formulations were corn starch, SSG and MCC. The superdisintegrants were sieved through a No. 10 mesh before adding to the formulation. The cocoa butter was grated into small particles and melted in a hot water bath at a temperature of 35°C. The superdisintegrants were incorporated into the melted cocoa butter and stirred until uniformly mixed. A PVC mold was lubricated using castor oil. A 300 mg mixture was poured into the lubricated mold and refrigerated at 5°C for 4 hours. The solidified cocoa butter FMTs were stored in a desiccator and maintained at room temperature until further analysis.

Table 1 Formulations of cocoa butter based FMTs

FORMULATION	COCOA BUTTER (mg)	STARCH (mg)	MCC (mg)	SSG (mg)	TOTAL
1	300	-	-	-	300 mg
2	270	30	-	-	
3	240	60	-	-	
4	210	90	-	-	
5	270	-	30	-	
6	240	-	60	-	
7	210	-	90	-	
8	270	-	-	30	
9	240	-	-	60	
10	210	-	-	90	

Physical tests

Hardness test

Ten FMTs were crushed using a Hardness tester machine, Model EBT-2PL Electrolab (Malaysia). The mean crushing strength was calculated (15).

Weight variation test

Twenty FMTs were weighed individually using a Scout Pro Ohaus electronic analytical balance, d=0.01 g. The mean weight and standard deviation were calculated (16).

Thickness test

The thickness of ten FMTs were measured using an Electrolab thickness/hardness tester. The mean thickness, and standard deviation were calculated (16).

Friability test

Twenty FMTs were weighed. They were placed in a friabilator drum Model FRV 200U, Copley and rotated at 25 RPM for 4 minutes. The FMTs were de-dusted and reweighed (17).

Disintegration time test

Six FMTs were individually placed in each of the six tubes of the basket. The basket rack was positioned above a 1 liter beaker containing distilled water at 37°± 1°C. The apparatus was started, and the time taken for all of the six tablets to completely disintegrate was recorded (18).

Selection of optimum formulation

The formulation with the fastest disintegration time and greatest hardness was determined to be the optimum formulation.

Physical characterization test and stability study for the final formulation

A stability study was carried out for the optimum formulation by storing the tablets for 9 months at 30±1°C. The tablets were sampled at the end of the 1st, 3rd and 9th month. They were characterized using the physical characterization tests described previously.

Statistical analysis

The data was analyzed using Statistical Procedure for Social Science (SPSS) version 23. The data was subjected to one-way analysis of variance (ANOVA) to determine significance. The results were expressed as mean ± SD. The confidence level was set at 95%.

RESULTS

Melting point of cocoa butter

The DSC thermogram for cocoa butter is shown in Figure 1. The cocoa butter showed an endotherm at 34.7°C (19).

Physical characterization tests for cocoa butter based FMTs

The results of the physical characterization tests for the FMTs containing the cocoa butter are shown in Table 2.

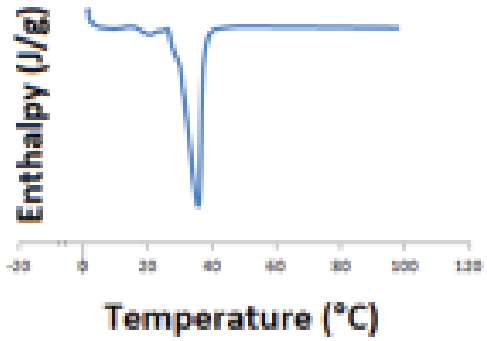

Figure 1 DSC thermogram of cocoa butter. Melting point = 34.68°C

Hardness test

The results of the One-Way ANOVA tests suggested that at least one pair among the FMT formulations showed a significantly difference. Based on the Tukey post-hoc test analysis, the hardness of formulation F7 was significantly different. The hardness was directly proportional to the percentage of superdisintegrants used in the formulation.

Weight variation testing

The results of One-Way ANOVA tests showed no significance.

Thickness test

The result of the One-Way ANOVA test suggested

Table 2 Results of physical characterization of various FMT formulations.

FORMULATION	HARDNESS (kg)*	WEIGHT (g)**	THICKNESS (mm)*	FRIABILITY (%)**	DISINTEGRATION TIME (s)***
F1	0.57 ± 0.16	0.32 ± 0.02	4.70 ± 0.14	0.31	260 ± 34.64
F2	0.50 ± 0.17	0.31 ± 0.01	4.69 ± 0.14	0.46	198 ± 27.54
F3	0.52 ± 0.15	0.32 ± 0.02	4.69 ± 0.13	0.31	171 ± 7.81
F4	0.79 ± 0.33	0.31 ± 0.02	4.59 ± 0.09	0.31	156 ± 5.29
F5	0.68 ± 0.41	0.31 ± 0.02	4.71 ± 0.13	0.48	175 ± 5.00
F6	1.21 ± 0.91	0.31 ± 0.01	4.59 ± 0.07	0.32	148 ± 12.58
F7	1.30 ± 0.53	0.32 ± 0.01	4.62 ± 0.08	0.16	103 ± 4.16
F8	0.59 ± 0.28	0.32 ± 0.01	4.80 ± 0.09	0.97	158 ± 6.80
F9	0.83 ± 0.27	0.31 ± 0.02	4.62 ± 0.13	0.82	142 ± 7.64
F10	0.84 ± 0.34	0.31 ± 0.01	4.60 ± 0.03	0.64	130 ± 5.00

*Tests where n = 10
**Tests where n = 20
***Test where n = 6

that there was at least one pair among the FMT formulations that showed a significant difference.

Friability test

Friability was <1% for all the formulations. Increasing the percentage of superdisintegrants, decreased the friability within the limits determined for this study.

In-vitro disintegration time test

The result of the One-Way ANOVA test suggested that there was at least one pair among the FMT formulations that showed a significant difference. The disintegration time for formulation F7 was significantly faster than those of the other formulations (except for F9 and F10). Increasing the percentage of superdisintegrants, reduced the disintegration time within the limits used in this study.

Selection of optimum formulation

Based on the greatest hardness, lowest friability and the fastest disintegration time, formulation F7 was chosen as the optimum formulation.

Stability study

The results of the stability study are presented in Table 3. The results of ANOVA suggested that there were no significant differences between the various physical parameters at any time interval during the stability study.

DISCUSSION

Hardness test

Tablets with sufficient hardness can withstand the mechanical stresses and strains during manufacturing, packaging and shipping processes. However, if the tablets are too hard they may have slower rates of disintegration and dissolution. It is therefore important to maintain the hardness of the tablets within an acceptable range (18).

As the percentage of superdisintegrants increased, the hardness of the FMTs increased. Formulation F7 (containing 30% MCC) showed the greatest hardness (1.30 ± 0.53 Kg). Increasing the percentage of MCC from 10 to 30% in the formulation increased the hardness of the FMTs. MCC was used as a binder in the table formulations due to its superior dry binding properties. The binding properties of MCC increased the hardness of the FMTs (20).

The hardness of the FMTs increased with increasing percentage of SSG. However, the increase was not as prominent as for the formulations containing MCC. SSG provides binding properties in the tablets which can improve the hardness through the removal of moisture (21-22).

Weight variation test

Weight uniformity can affect the uniformity of a tablet content (15). All the batches in this study passed a

Table 3 Stability study results

PARAMETER	F7				ANOVA
	0-MONTH	1-MONTH	3-MONTH	9-MONTH	
Hardness (Kg)*	1.30 ± 0.50	1.31 ± 0.57	1.21 ± 0.46	1.25 ± 0.48	P = 0.148
Weight variation (g)**	0.32 ± 0.02	0.32 ± 0.01	0.32 ± 0.01	0.32 ± 0.01	P = 0.566
Thickness (mm)*	4.62 ± 0.09	4.61 ± 0.10	4.61 ± 0.12	4.61 ± 0.09	P = 0.689
Friability (%) **	0.16	0.20	0.21	0.22	-
Disintegration time (s)***	103.00 ± 4.16	106.33 ± 1.15	102.33 ± 2.35	110.54 ± 3.51	P = 0.210

*Test included 10 tablets

**Test included 20 tablets

***Test included 6 tablets

weight variation test (3) as the weight of the tablets were within the range of ± 7.5%.

Thickness test

The thickness of the tablet is one of the dimensional variables related to the compression process (16). Tablet thickness is typically controlled within a ±5% variation, in part to facilitate packaging (23). The thicknesses of all FMTs batches in this study were within the range of ± 5%.

Friability test

The friability test is indicative of the ability of the FMTs to withstand abrasion during packaging, handling and shipping. A typical maximum weight loss is <1% (18), which was met by all the FMTs used in the study.

It was observed that friability decreased with an increase in the percentage of superdisintegrant. This might be due to the increase of FMTs hardness with increasing amounts of superdisintegrants (23).

Disintegration test

A tablet must disintegrate in order to release the API from the dosage form. Disintegration time is thus an important physical parameter because it may influence the bioavailability in immediate release dosage forms. Disintegration time measures the time required for tablets to disintegrate in solution under a given set of conditions (18).

The superdisintegrant was added to the formulation to accelerate the disintegration of FMTs when they came into contact with a fluid or aqueous medium. The disintegration times for all batches (excluding F1 and F2) were within 3 minutes. MCC causes disintegration by capillary action. Water enters the tablet matrix through the capillary pores. In this study, formulation F7 contained 30% MCC. It is suggested that formulation F7 disintegrated through two mechanisms, namely the amorphization of cocoa butter and the capillary effect of MCC (24).

SSG causes disintegration of a tablet though a swelling mechanism. SSG has the capability to absorb water and swell to about 300 times its original volume when coming into contact with an aqueous medium (22). As a result, SSG contributed to rapid disintegration and increased the dissolution of the FMTs.

Starch forms pathways throughout a tablet matrix that enable water to be pulled into the structure through capillary action, thus resulting in a disruption of the tablet matrix (24). The formulations containing corn starch showed a longer disintegration time compared to the formulations containing SSG. This could be because SSG has a greater swelling capacity than corn starch (22).

Formulation F7 contained 30% MCC and 70% cocoa butter. Cocoa butter melts at body temperature. MCC has the ability to draw water into the tablet matrix to increase the effective surface area for water exposure. It is suggested that the disintegration of formulation F7 FMT was a synergy between the amorphization of the cocoa butter and the capillary effect of MCC.

Selection of optimum formulation

Formulation F7 (containing 30% MCC) was chosen as the optimum formulation. This formulation showed the fastest disintegration time, the lowest friability and the greatest hardness.

Stability study

No significant difference was found in the physical characterization parameters after storage at 30 ± 1°C for 9 months. The stability study did not measure the chemical incompatibility between the cocoa butter and the other ingredients using FTIR, hence there can be no assurance that chemical interactions between the various ingredients of the formulation did not occur during storage.

CONCLUSION

Formulation F7 containing 30% MCC was chosen as the optimum formulation. This API devoid formulation showed the fastest disintegration

time, greatest hardness and lowest friability. These parameters did not change upon storage at 30 ± 1°C for 9 months. The cocoa butter based FMT could serve as a convenient dosage form that does not have the friability, packaging or cost issues associated with ODTs, that need not be swallowed whole and where the API's taste is relatively innocuous. Further studies are needed to ascertain whether the incorporation of API changes or invalidates this optimum formulation as regards physical and functional properties, including polymorphism of the cacao butter and whether the excipients and API are chemically stable upon storage.

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