

DISINTEGRANT PROPERTIES OF A PARACETAMOL TABLET FORMULATION LUBRICATED WITH CO - PROCESSED LUBRICANTS

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Abstract

In this study, cocoa butter co - processed with a combination of magnesium stearate and talc (CMT) was evaluated as a lubricant in a paracetamol tablet formulation. In the evaluation study the disintegrant properties - tablet disintegration time (DT) and crushing strength friability/disintegration time ratio (CSFR/DT) of paracetamol tablets prepared from granules lubricated with CMT were compared with tablets prepared from granules lubricated with combination of magnesium stearate and talc (MT) alone. The study reveals that the lubricant type and concentration influenced the disintegrant properties, and that the co - processed lubricant could be useful in situations where a low CSFR/DT ratio is required e.g. sustained release tablets.

Rezumat

În studiul experimental prezent s-au evaluat caracteristicile de lubrefiere ale untului de cacao co-procesat cu un amestec de stearat de magneziu și talc, în formularea comprimatelor cu paracetamol. A fost efectuat un studiu comparativ cu comprimate de paracetamol în a căror formulare s-a folosit amestecul de stearat de magneziu și talc.

Key words: Cocoa-butter; lubricant; magnesium stearate; talc; crushing strength; friability; disintegration time.

Introduction

In tablet compression, lubricants are used in powder form to reduce frictional forces at the interface between powder, granule and tablet surface with the die wall [1]. Lubricants can also help to reduce the sticking of tablets to punches in the tableting machine and the wear of tooling; they improve the flow and filling of substances into the cavities [2,3]. Most powder lubricants have these properties, but to varying extents, an ideal lubricant displaying all desirable properties has not been found yet [4]. The type, concentration, method of incorporation, time and conditions of mixing, and efficiency of lubricants affect many properties of the produced tablets such as tablet weight, crushing strength, friability, disintegration time and even stability [2, 5, 20, 21].

Recent studies on tablet formulation suggested that conventional lubricants such as magnesium stearate and talc impart some undesirable characteristics to tablets like significant reduction in crushing strength [6] and significant decrease in disintegration time [1] because of the weak binding force of magnesium stearate with other particles. Hence, it is necessary to search for alternative lubricants, either through new 'ideal' substances or coprocessing a new substance like cocoa butter with already existing lubricants.

Cocoa butter is a lipid material obtained from the roasted seed of *Theobroma cacao*. It is slightly soluble in 95% alcohol and freely soluble in ether, chloroform and light petroleum. It melts at a temperature below human body temperature. A previous report [7] on the use of co – processed cocoa butter as lubricant in a tablet formulation suggested that it would influence the compressional and mechanical properties of a tablet formulation. Hence, the purpose of this work was to co - process cocoa butter a cheap and easily available lipid with a 50:50 mixture of magnesium stearate and talc (MT), elucidate the effect of cocoa butter on the lubricant activity of MT in a paracetamol formulation, and to evaluate the influence of the changes in the concentration of lubricant on the disintegrant properties of tablets produced. This study could provide relevant information on the lubricant activity of cocoa butter on disintegration of tablets.

Disintegrant properties are determined by measuring disintegration time and correlation with the friability and crushing strength of tablets. These parameters will then be used to quantify the crushing strength-friability/disintegration time (CSFR/DT) of the tablets. The CSFR/DT is used for evaluating the balance between the binding and disintegration properties of a tablet [8, 9, 19].

Materials and methods

Materials

The materials used were paracetamol powder BP, corn starch BP (BDH Chemicals Ltd, Poole, UK), Lactose BP (AB Knight and Co., London, UK), Cocoa - butter (Witco Corp., Organics Division, Chicago, USA), Magnesium stearate and Talc (BDH Chemicals Ltd; Poole, UK), Acetone (BDH Chemicals Ltd; Poole, UK) and 95 % Ethanol obtained from Sigma – Aldrich Laborchemickalien GMBH, Seelze, Germany.

Preparation of processed powdered lubricant mixture

Equal amounts of magnesium stearate and talc were triturated together using a porcelain mortar and pestle for a period of 5 min to ensure a

uniform mixing of the two powders (lubricants). The mixture was sieved using mesh 100 (150 μm) sieve and then stored in a screw-capped bottle until needed.

Cocoa – butter was co – processed with MT as reported earlier [7] i.e. cocoa butter weighing 1.20 g was placed inside a beaker containing 250 mL of 95% ethanol. This was then placed in a water bath set at 60°C, to allow the melting and dissolving of cocoa butter in the ethanol. Magnesium stearate – talc mixture (MT) weighing 38.8 g was added and mixed with the ethanolic solution of cocoa butter in the beaker. The mixture (CMT) was placed in the dessicator for 72 h to allow for the ethanol to evaporate off. The remaining mix contains 3.0% w/w of cocoa-butter in the total mixture (this % w/w is the optimum concentration obtained in the preliminary studies). The processed powdered lubricant mixture was then stored in a screw – capped bottle until ready for use.

Preparation of granules

The wet granulation method of massing and screening was used. A 1500 g batch of formulation of paracetamol (85 %w/w), corn starch (5 %w/w) and lactose (10 %w/w) was dry mixed in a Hobart planetary mixer (Hobart Canada Inc., Don Mill, ON, Canada). This was moistened with the appropriate amount of starch binder. Massing was continued for 5 min and the wet mass was granulated using a sieve size 16 (1000 μm) attached to an Erweka (Model AR 400) granulator (Erweka Apparatebau GmbH, GmbH Heusenstammkr. Offebach/main/Germany). The resulting granulation was then dried in a hot air oven. The dried granulation was screened through a mesh 16 (1000 μm) to produce the required uniform size of granules. The granules obtained were then divided into 13 equal parts before addition of lubricant into each part [19, 20].

Addition of lubricants to the granules

The lubricant was not added to the first part of the granulation which serves as control sample, while granulations in parts 2 - 7 were mixed with different concentrations (0.5 % w/w, 1.0 % w/w, 1.5 %w/w, 2.0 % w/w 2. 5 %w/w and 3.0 %w/w) of magnesium stearate – talc (MT) lubricant mixture to produce the respective batches (2 – 7) of granulation. The bottles containing the lubricated mixtures were then gently shaken for ten minutes to ensure proper mixing. The same method was used for adding cocoa butter treated magnesium stearate plus talc (CMT) to granulation parts 8 - 13 to produces batches 8 - 13.

Granular density of each batch was determined by the pycnometer method with acetone as displacement fluid.

Preparation of tablets

Quantities (550mg) of granules from each batch were compressed into tablets with three predetermined loads (25, 50 and 75 – Kpcm⁻²) on a Pharma 100 multi station rotatory tablet press (Korsch Maschinen Fabrik, Berlin, Germany) with a 10.5mm die and flat-faced punch assembly. A set of tablets was produced from each pressure. After ejection, the tablets were stored in airtight containers to allow for elastic recovery and hardening, and prevent falsely low yield values before the tablets were subjected to analysis. Their weight (w) and dimension were then determined to be within ± 0.01 mg and 0.01mm respectively, and their relative density (RD) was calculated using the equation:

$$RD = m/V_t\rho_s \quad (1)$$

where V_t is the volume (cm³) of the tablet and ρ_s is the particle density (1.329 – 1.517) of solid material. The volume reduction, which increased with the successive increase in the compression pressure, led to variable relative density.

Disintegration test

The disintegration time (DT) of the tablet was determined in distilled water at $37 \pm 0.5^\circ\text{C}$ in a BP Manesty six station disintegration test unit (Manesty Machines Limited, Liverpool, UK). Tablets were placed on the wire mesh just above the surface of the distilled water in the tube. The time taken for each tablet to disintegrate and all the granules to go through the wire mesh was recorded. Results were expressed as an average of three determinations.

Determinations of tablet crushing strength and friability

A Monsanto hardness tester (Monsanto Chemical Corp, USA) was used at room temperature to determine the load required to diametrically break the tablet (crushing strength) into two equal halves. Tablets with signs of lamination and capping were not used.

The friability of the tablets was determined using a Roche friabilator (Erweka Apparatebau, Germany) operated at 25-rev min⁻¹ for 4 minutes. Ten tablets were used at each relative density. The average of four determinations was taken for the crushing strength and friability values. Statistical analysis (standard error of the mean at a confidence level of 0.95) of the results in Table 1 revealed the low variability of the results obtained.

Results and discussion

The disintegrant properties of pharmaceutical tablets are quantifiable by the crushing strength, friability, disintegration time and crushing strength-friability/ disintegration time ratio. Crushing strength

provides a measure of tablet strength while friability is a measure of tablet weakness [10, 11, 12]. There is no official requirement for crushing strength and friability in the British Pharmacopoeia [13] probably because, in case of crushing strength, the desired crushing strength is largely dependent on the intended use of the tablet [14]. Representative plots of the crushing strength *versus* the relative density of paracetamol tablets at a concentration of 2.5 % w/w lubricant mixtures are shown in Figure 1.

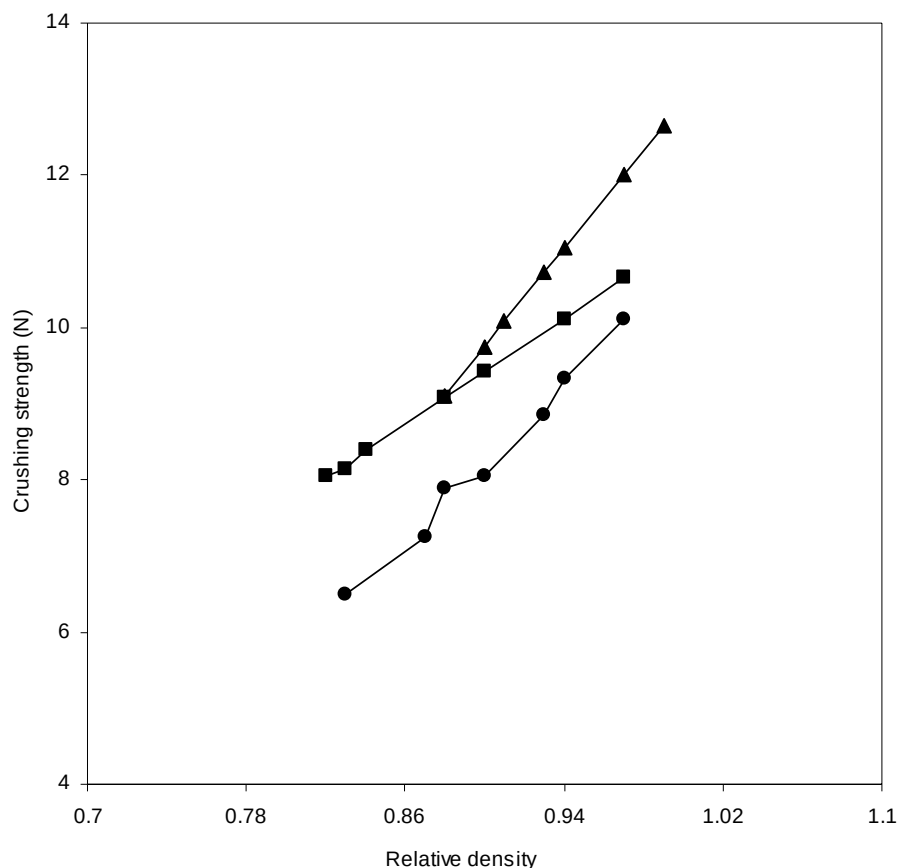


Figure 1
Representative plots of crushing strength versus relative density (g/cm^3) for paracetamol tablets containing 0.0 %w/w lubricant, ▲, 2.5 % MT, ● and 2.5 %w/w CMT, ■

It is observed from the figure that as the relative density increased, the crushing strength of the tablets increased. This could be due to the decrease in porosity and subsequent increase in the number of contact points, hence, an increase in the degree of bonding between the particles [10, 11].

Table I

Values^a of a crushing strength (CS), disintegration time (DT), friability (FR) and crushing strength – friability/disintegration time ratio (CSFR/DT) of paracetamol tablets

Lubricant	Concentration (% w/w)	CS (N) ^b	DT (min) ^b	FR (%) ^b	CSFR/DT
None	0.0	9.75 (0.01)	4.34 (0.03)	5.69 (0.07)	0.394
Magnesium	0.5	9.08 (0.05)	1.08 (0.06)	2.42 (0.03)	3.091
Stearate + Talc	1.0	7.51 (0.02)	0.50 (0.06)	2.09 (0.06)	7.186
	1.5	7.70 (0.02)	0.38 (0.08)	2.02 (0.10)	10.031
	2.0	7.87 (0.01)	0.28 (0.02)	2.70 (0.06)	10.410
	2.5	8.05 (0.05)	0.26 (0.10)	2.85 (0.07)	10.863
	3.0	8.40 (0.06)	0.21 (0.08)	2.97 (0.02)	13.347
Cocoa butter	0.5	8.68 (0.11)	1.69 (0.06)	3.13 (0.11)	1.640
treated +	1.0	8.95 (0.14)	1.15 (0.08)	5.46 (0.11)	1.425
Magnesium	1.5	9.55 (0.09)	1.21 (0.08)	7.57 (0.16)	1.042
stearate +	2.0	10.22 (0.11)	1.28 (0.12)	10.84 (0.14)	9.736
Talc	2.5	11.42 (0.09)	1.53 (0.11)	17.44 (0.18)	0.428
	3.0	11.49 (0.08)	5.54 (0.05)	39.56 (0.09)	0.052

a = Relative density of 0.90

b = Mean ± SEM, n = 3

From Table I, it can be seen that the crushing strength of tablets produced from granulations lubricated with CMT were higher than those of tablets produced from granulations lubricated with MT. This could be due to the fact that there were more particle – particle contact points, particularly with cocoa butter, a semi-solid fat which facilitates asperitic melting and hence, would lead to higher crushing strength values obtained. It was also observed that the crushing strength values increased as the concentration of lubricants increased.

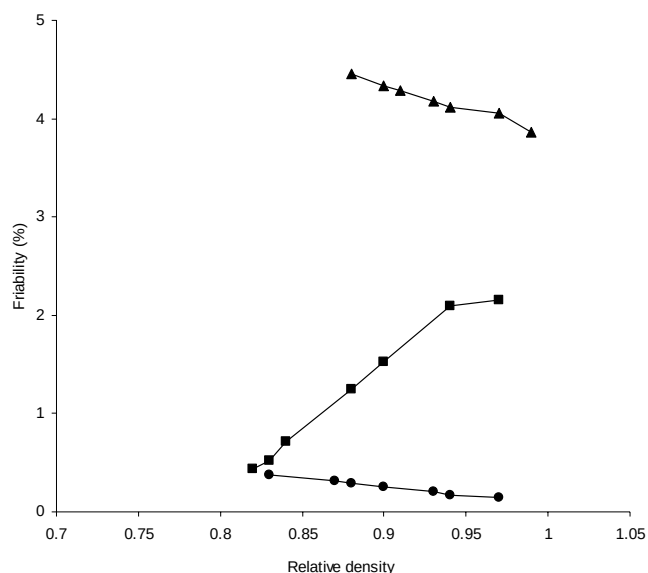


Figure 2

Representative plots of friability versus relative density (g/cm^3) for paracetamol tablets containing 0.0 %w/w lubricant, ▲; 2.5 %w/w MT, ● and 2.5 %w/w CMT, ■.

Figure 2 shows representative plots of the friability versus relative density for the paracetamol tablets containing the lubricants at a concentration of 2.5 %w/w. It is seen that for 0.0 %w/w lubricant concentration and 2.5 %w/w, MT, the friability values decreased with the increase in relative density while for 2.5 %w/w CMT, the friability values increased. This observation could be due to the influence of forces of attraction in the tablet mass. For tablets with MT apart from cohesive and adhesive forces operating between the granules to form a tablet mass, van der Waal's forces of attraction would also come into play because of the particle size of the lubricant than in the case of tablets containing CMT with a higher particle size). Hence, with the increase in relative density, the influence of van der Waals forces in the tablet mass is felt as a subsequent reduction in friability values. Table I shows the effect of the increase in concentration of lubricant on the friability values. Generally, for tablets lubricated with MT, there was

registered a reduction with the increase in the lubricant concentration while for tablets lubricated with CMT an increase was observed. This could be due to the observed result in the case of the relative density versus friability.

The disintegration time of the paracetamol tablets obtained generally showed an increase with the increase in the relative density of the tablets. Representative plots at a concentration of 2.5 %w/w of lubricants are shown in Figure 3. Observations were similar to those previously made by researchers [10, 15]. The increase in the relative density there is usually accompanied by a decrease in porosity [16, 17]. Consequently, water penetration into tablets would slow down, swelling of disintegrants would be reduced and the development of the active mechanism of disintegration would also be reduced. When porosity decreases more solid bridges are formed, which would make the annihilation of interparticulate forces more difficult [12, 18]. From Table I, it is seen that the disintegration time generally increased with the increase in lubricant concentration. Tablets lubricated with CMT showed a significantly higher disintegration time than tablets lubricated with MT. This could be due to asperitic melting of cocoa butter that would assist in bridging the gap between particles [8], and hence lead to an increase in the area of contact between particles thereby reducing the rate of liquid, penetration into the interstitial void spaces.

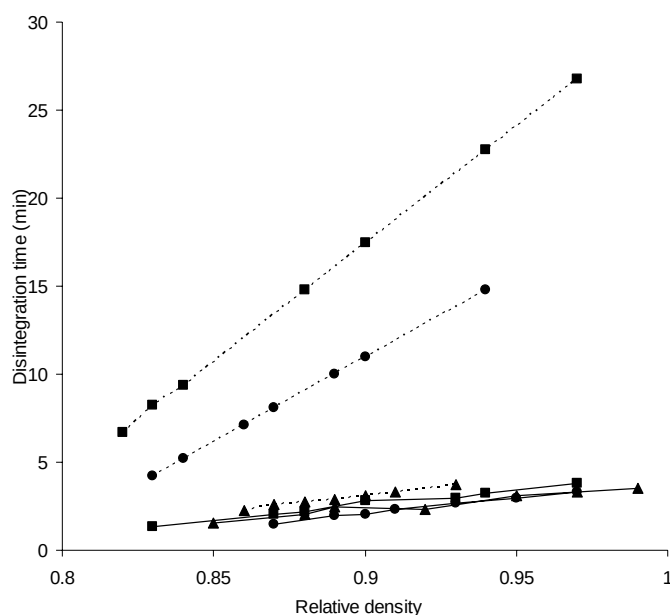


Figure 3

Effects of relative density (g/cm^3) on disintegration time for paracetamol tablets containing different concentrations of lubricants: $\blacktriangle$ - 0.5 %w/w, $\bullet$ - 1.4 %w/w, $\blacksquare$ - 2.5 %w/w ; (----) - MT, (.....) - CMT

This result in reduction of the swelling of the disintegrant present and disruption of the tablet is reduced. Hence, a higher disintegration time than tablets containing MT.

The crushing strength friability/disintegration time ratio (CSFR/DT ratio) has been suggested as a better index for measuring tablet strength (crushing) and weakness (friability), it simultaneously evaluates all negative effects of these parameters on disintegration time [8, 9]. A higher value of CSFR/DT ratio indicates a better balance between binding and disintegration properties. Generally, the higher the CSFR/DT values the better the disintegration of the tablet.

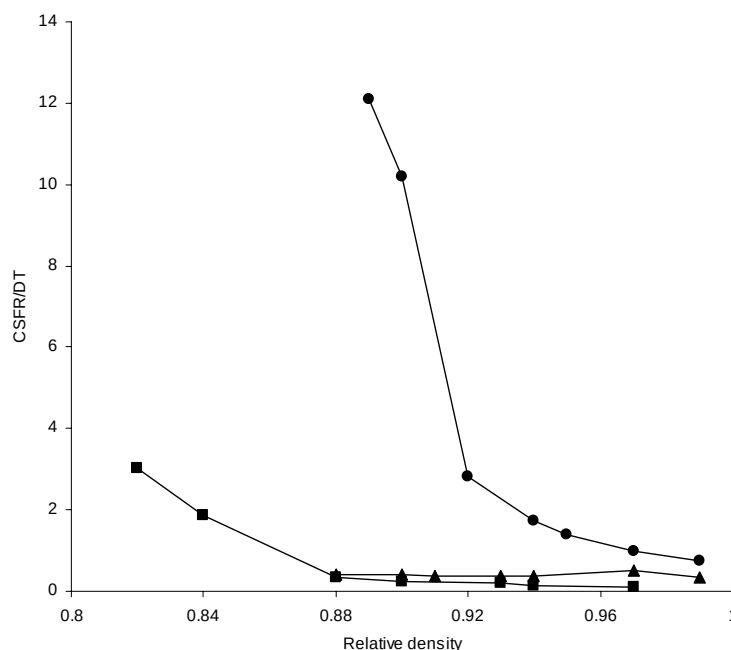


Figure 4

Representative plots of CSFR/DT versus relative density (g/cm^3) for paracetamol tablets containing 0.0 %w/w of lubricant, ▲ ; 2.0 %w/w of MT, ● and 2.0 %w/w of CMT, ■.

From the values shown in Table I, it is observed that the values of CSFR/DT for tablets containing CMT are lower than those of tablets containing MT. Representative plots of CSFR/DT *versus* relative density for paracetamol tablets containing 0.0 %w/w and 2.5 %w/w lubricant are shown in Fig 4. Higher values of CSFR/DT obtained for tablets lubricated with MT implies that the tablets will have better disintegration properties than the tablets lubricated with CMT. This is not unexpected since cocoa butter is a

lipid substance and, which would simultaneously reduce penetration of the disintegration fluid into the tablet mass while bridging the gap between particles leading to increased bonding. These simultaneous processes would lead to a poor balance between hardness and disintegration properties. The relative density of tablets also affected the CSFR/DT, with the increase in the relative density leading to a low value of CSFR/DT. This is reflected in Figure 4. It could be due to the formation of more solid bonds and reduced porosity with increase in the relative density. This would lead to higher crushing strength and ultimately longer disintegration time.

Conclusion

This study concludes that the use of co - processed cocoa butter with combination of magnesium stearate and talc would affect the properties of the tablets produced particularly the crushing strength and disintegration time. The results also show that the type of lubricant, concentration of lubricant and relative density of the tablets affected the CSFR/DT of the tablets. Furthermore, the study revealed from the CSFR/DT values that cocoa butter, if co processed with a combination of magnesium stearate and talc, may not be useful as a lubricant in particular situations where a higher CSFR/DT i.e. lower disintegration time is required, but may be useful in situations where a higher crushing strength and disintegration time is required e.g. in sustained release tablets.

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