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Cetirizine Dihydrochloride Tablets Comprising Two Different Lubricants with Highly Loaded Colloidal Silicon Dioxide

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Abstract

Recently, the fast disintegrating tablet (FDT) has started gaining popularity and acceptance as new drug delivery system. Cetirizine dihydrochloride (CD) is the selective histamine (H-1)-receptor antagonist that is demonstrated to treat the symptoms associated with seasonal and perennial allergic rhinitis which this drug nowadays was prepared in form of FDT. Lubricant typically influences on tablet disintegration time (DT) and wetting time (WT). Therefore, it is important for optimizing the lubricant amount in this dosage form. The purpose of this study was to evaluate the effect of the lubricants (magnesium stearate (Mg-st) and sodium stearyl fumarate (SSF)) on the CD tablet containing highly loaded colloidal silicon dioxide. Mg-St was well known as a high hydrophobic lubricant and that sodium stearyl fumarate (SSF) is less hydrophobic than Mg-St. Therefore, the DT and WT of tablets containing Mg-St increased as the amount of Mg-st increased. However, the DT and WT of FDT were influenced not only by lubricant properties, but by hardness. The polarity of the surface tablets was remarkably decreased by increased the amount of Mg-st which related to the WT of FDT. Therefore, the contact angle of tablets increased and SFE decreased. On the other hand, the polarity of the surface tablets was remarkably increased by increased the amount of SSF.

Key words: Cetirizine dihydrochloride, Magnesium stearate, Sodium stearyl fumarate, Highly loaded colloidal silicon dioxide

Introduction

Cetirizine dihydrochloride (CD) is the selective histamine (H-1)-receptor antagonist that is demonstrated to ease the symptoms associated with seasonal and perennial allergic rhinitis.[1, 2] CD is water soluble drug (pKa 8.3).[3] Fast disintegrating tablet (FDT) of CD can be better alternative to conventional tablets for allergic patient. Recent developments in the fast disintegrating tablet (FDT) provide a convenient solution for patients who have difficulties in swallowing tablets and other dosage forms.[4, 5, 6] The FDT dissolves or disintegrates in the saliva within a matter of seconds when placed upon the tongue and then it is swallowed to the stomach.[7] The dosage form which can be taken without water is useful in the case of the acute onset of a symptom.[8, 9]

Practically, the basic tablet excipients include binders, diluents, disintegrants, glidants and lubricants. Lubricants are added in the final steps of mixing formulation components prior to compression. Lubricants practically prevent adhesion of compacts to the surface of the punches and dies during compression and ejection from the die cavity. Lubricants can influence on disintegration time (DT), hardness and dissolution of prepared tablets.[10, 11] Too much lubricant, however, will cause the powder to form globules and to resist the proper cohesion. Magnesium stearate (Mg-st) has been widely used as the lubricant in tablet production. Over the years, there have been many reports that extending this film, through either an increase in the amount of Mg-st or a longer mixing time, has a negative effect on the hardness, friability, and DT of the tablets. Because the bonds between Mg-st particles are weaker than those between unlubricated excipient particles, a more extensive coverage of the excipient particles by Mg-st will lead to a decrease in tablet hardness. This decrease in hardness may also lead to an increase in tablet friability.[12-14] Along with a decrease in tablet hardness, most authors report that an increase in the amount of Mg-st leads to an increase in tablet DT.[15] This is due to the hydrophobic nature of the Mg-st molecule and, by extension, of the lubricant film, which hinders the penetration of water in the

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tablet. Sodium stearyl fumarate (SSF, Alubra®) is the fatty acid esters. Compared to Mg-st, this lubricant shows less interference with tablet strength and has a less negative effect on tablet disintegration and dissolution because of its hydrophilic nature.[16] Structures of Mg-st and SSF are depicted in Figure 1.

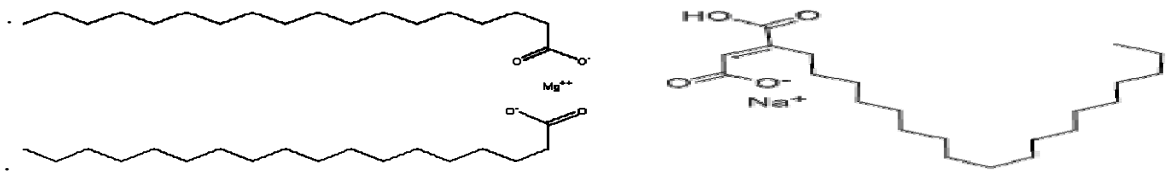

Figure 1. Structure of magnesium stearate (Mg-st)(left) and sodium stearyl fumarate (SSF, Alubra®)(right)

Colloidal silicon dioxide such as Aerosil 200 is hydrophilic glidant incorporated into solid dosage forms to improve the flow properties of cohesive powders. It decreases the weight variation and minimizes the tendency of powder components to separate or segregate from excessive vibrations.[17] Aerosil 200 can be employed as gelling agent for hydrophobic dispersed medium[18]. The high loaded Aerosil 200 in tablet was employed in this study since the tablet prepared with direct compression technique had the possibility of particle segregation.

Glidant and lubricant can greatly increase hydrophobicity (the resistance of a particle to absorb water). When a tablet does not allow the solvents to penetrate, it will have a slow disintegration, or dissolution rate. Tablets exhibiting this dilemma will have a high activation delay-time and their bioavailability can be decreased.

It is important to optimize the concentration of lubricants in formulation. It is mainly important to maintain the fast disintegration properties of tablets with a sufficient hardness. Therefore, the purpose of this study was to evaluate the effect of the type and amount of lubricant on the tablet characteristics of FDT prepared by direct compression. The lubricants used in this study were magnesium stearate (Mg-st) and sodium stearyl fumarate (SSF, Alubra®)

Materials and Experimental Procedures

Materials

CD and Avicel PH 101, magnesium stearate were donated from Pharmanueva Co., Ltd., Bangkok, Thailand. Aerosil 200 was purchased from Wacker-Chemie GmBH, Germany. Sodium stearyl fumarate (SSF, Alubra®) was donated from Onimax Co., Ltd., Bangkok, Thailand. Ludiflash® was gifted from BASF, Bangkok, Thailand. Na_2HPO_4, KH_2PO_4, NaCl, formamide were purchased from Ajax Finechem, Auckland, New Zealand. Ethylene glycol was purchased from Poch, Poland.

Methods

Preparation of cetirizine dihydrochloride fast disintegrating tablet

The composition of prepared tablets is shown in Table 1. The 5% CD FDT formulation was used in this study. Tablet ingredients were accurately weighed as mentioned in Table 1. Direct compression method was used to prepare the tablet because of its ease manufacture and low cost. Drug and all the excipients except Mg-st and SSF were mixed in mortar and pastle by geometric dilution. Finally, magnesium stearate and SSF were added into this blend and mixed properly again for 3 min. The blend was compressed using hydraulic press (SPECAC 15011, A Cambridge Electronic Industries Company, Kent England) to produce tablets weighing 200 mg each with a diameter of 9.53 mm with the compression force of 1 ton/cm^2.

Table 1. Composition of CD FDTs

Formula	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
CD	10	10	10	10	10	10	10	10	10	10	10	10
Ludiflash®	160	160	160	160	160	160	160	160	160	160	160	160
Avicel PH 101	20	19.5	18	16.5	15	12.5	10	19.5	19	18.5	18	15.5
Aerosil 200	10	10	10	10	10	10	10	10	10	10	10	10
Mg-st	-	0.5	2	3.5	5	7.5	10	-	-	-	-	-
SSF	-	-	-	-	-	-	-	0.5	1	1.5	2	4.5
weight/tab	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation

Weight Variation

The weight variation test was performed on 20 randomly collected tablets from a batch. The procedure described in USP 30 NF 25 was followed for this test[19]. Weight variation test was done by weighing 20 tablets individually.

Hardness, Thickness, Diameter

The hardness, thickness and diameter of tablets were measured using a hardness tester (Erweka® TBH 225 Heusenstamm, German) and the data reported was the mean of ten individual determinations.

Wetting Time (WT)

The 10 mL simulated saliva fluid was added to the petri dish with the diameter of 10 cm. A tablet was carefully placed in petri dish. The time required for the simulated saliva fluid to appear on the upper surface of tablet was noted as wetting time (n=6).[20]

Disintegration Time (DT)

The time required for disintegration of six tablets, placed in each tube of disintegration apparatus, was measured at 37±2°C using 900 ml simulated saliva fluid. The time for the tablet to completely disintegrate into fine particles was noted.

Contact Angle and Surface Free Energy (SFE)

Knowledge of the wettability and surface free energy of pharmaceutical solids is very important in the design of pharmaceutical formulation. Since lubricants form a hydrophobic membrane on the surface of the powder particle, the wettability and surface free energy of tablets are assessed by contact angle measurement. The method of assessing the surface free energy indirectly from wettability measurement is widely used. The wettability and SFE of tablets were determined by contact angle measurement which was carried out by the liquid drop on the tablet surface using the drop shape analysis method on the goniometer (FTA 1000, First Ten Angstroms, USA) with the pump out rate of 2.5757 ul/s. A stainless tube packed with the mixture was lowered into liquid and the recording of the contact angle was started when the liquid contacted with the tablet at 1 second (n=6). Distilled water, formamide, ethylene glycol were used as test solvents which had the different polarities. The SFE of tablets was calculated by Wu harmonic method[21]. In the method of Wu, the surface free energy is taken as the sum of the dispersive (γ^d) and the polar (γ^p) components. The surface free energies of solid materials can be determined by means of contact angle measurements, using two liquids (water and formamide were used as the solvent in this study) with known polarities. They can be assessed by solving an equation (1) with two unknowns:

$$(1+\cos\Theta)\gamma_l = \frac{4(\gamma_s^d\gamma_l^d)}{\gamma_s^d+\gamma_l^d} + \frac{4(\gamma_s^p\gamma_l^p)}{\gamma_s^p+\gamma_l^p} \quad \text{.....(1)}$$

where θ is the contact angle, γ_s is the solid surface free energy and γ_l is the liquid surface free energy.[22] The result of wettability and surface free energy studies were to understand the formation of the surface tablets which related to the disintegration and wetting time of FDT containing various lubricants.

Results and Discussion

Ludiflash® (containing mannitol, polyvinyl alcohol and crospovidone) is a new direct compressible excipient designed for FDT. It was utilized in the formulation as diluents with disintegrating property.[23] Avicel PH 101 was also included in the formulation as diluent. Colloidal silicon dioxide (Aerosil 200) acted as a glidant. It is known that Mg-St is hydrophobic and SSF is less hydrophobic than Mg-st.[2] All formulated tablets exhibited low weight variation that varies between 0.1948 g to 0.2004 g from different batches (Table 2). Thickness and diameter also showed low variation. The hardness of tablets containing Mg-st (A2-A5) seems to decrease as the amount of lubricant increased (Table 2) because the lubricant created a waxy covering and prohibited inter-particulate forces from bonding. The incorporation of 0.25-5% Mg-st decreased in the hardness of the tablets. This can be attributed to negation of the enhanced volume reduction and ability to consolidation by greater particle surface coating and subsequence interference in the bonding. Hardness of the tablets increased when concentration of Mg-st increased (A6, A7 compared with A2-A5). The increased hardness with increased levels of Mg-st can partially be explained on the basis of improved volume reduction and consolidation behavior. It may also be assisted by formation of new surface and denser compacts by bringing the particle surface areas into closer proximity and an increased ability to transmit the compression force resulting in more cohesive compacts. On the other hand, the hardness of tablets containing SSF did not depend on SSF amount.

Table 2. Physical properties of CD FDT

Formula	weight (mg)	thickness (mm)	diameter (mm)	hardness (N)	DT (second)	WT (second)
A1	200.54±1.16	2.21±0.01	9.60±0.00	137.5±17.19	389.67±25.53	93.33±5.79
A2	198.95±0.74	2.15±0.03	9.58±0.02	141.83±8.95	196±30.46	127.17±7.57
A3	199.61±0.56	2.14±0.03	9.59±0.01	133.17±13.91	230.38±29.12	136.5±7.71
A4	199.69±0.55	2.17±0.01	9.59±0.02	129.5±6.92	255.17±20.32	164.5±9.77
A5	200.01±0.46	2.14±0.04	9.59±0.02	127.5±5.82	255.17±2.04	178.83±13.26
A6	199.68±0.44	2.14±0.01	9.59±0.00	140±8.29	256.33±1.86	175.5±21.29
A7	199.82±0.33	2.12±0.01	9.59±0.01	135.33±6.31	288.32±11.36	180.33±15.98
A8	200.3±0.55	2.09±0.01	9.55±0.02	144.33±9.97	252.83±7.70	204.17±22.89
A9	199.64±0.70	2.12±0.02	9.59±0.01	122.17±26.00	205.17±25.46	195.17±4.49
A10	199.74±0.36	2.08±0.04	9.56±0.02	142.67±9.29	244.17±24.07	163±9.59
A11	199.53±0.55	20.8± 0.02	9.58±0.02	128.5±8.96	204.5±22.01	150±15.17
A12	199.5±0.30	2.12±0.02	9.61±0.01	102.67±6.19	171.17±4.45	113±8.34

DT and WT of tablets containing Mg-st increased as the amount of Mg-st increased. A possible explanation for this behavior was the formation of the hydrophobic membrane of Mg-st on the surface of the powder particles. Moreover, the DT and WT of tablets containing SSF seems to decrease as the amount of SSF increased owing to hydrophilic property of SSF. In addition, this is due to overriding influence of the strength of the interparticle bonds on the disintegration time of the tablets as well as on their hardness. We previously hypothesized that the DT and WT of the tablets containing Mg-st and SSF depended on only the properties of two lubricants. However, the DT and WT of tablets were influenced not only by lubricants properties, but by hardness. In the same amount of two lubricants (A2 and A8), the hardness of A2 was 148.83 N and that of A8 was 144.33 N. DT of A2 and A8 was 196s and 252.83s respectively. Moreover, the mechanical stress is applied, hardness or tensile strength of tablets is influenced by different factors such as, the elastic and plastic characteristics of the material. Furthermore, Mg-st and Aerosil® is enhance the hardness of tablets containing plastic deformation of the materials (Avicel®)[24]

The DT of A2-A12 (with lubricant) lower than that of A1 (without lubricant) because formulation of A1 comprised of water soluble diluent, glidant, disintegrant and water soluble drug, the DT of A1 tend to dissolve rather than disintegrate. When the tablet dissolved, it formed the layer film that impeded the disintegration of tablets.

Typically, the wettability of surface tablets could be described from the contact angle and SFE values. The hydrophilicity of the surface tablets was changed with increasing amount of Mg-st. The wettability of the surface, as expected. It can be supported by the poor wetting of magnesium stearate (contact angle with water). The contact angle of tablets containing Mg-St increased as the amount of Mg-st increased (Table 3)[22] whereas the contact angle of tablets containing SSF decreased as the amount of SSF increased (Figures 2 a and b). In addition, the SFE of tablets containing Mg-St decreased as the amount of Mg-st increased; nevertheless, the SFE of tablets containing SSF increased as the amount of SSF increased[22,25]. These result described that the polarity of the surface tablets was remarkably decreased by increasing the amount of Mg-st which related to the WT of FDT. Therefore, the contact angle of tablets increased and SFE decreased. On the other hand, the polarity of the surface tablets was remarkably increased by increasing the amount of SSF.

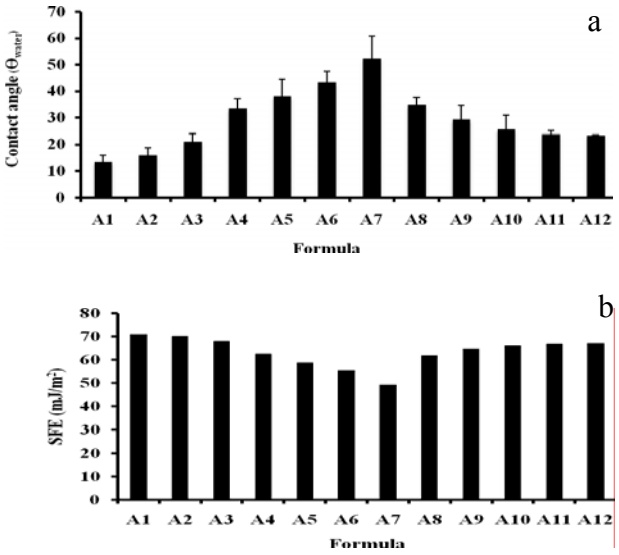

Figure 2. Effect of type and amount of lubricants on characteristics (a) contact angle (θ_{water}) and (b) SFE of tablets.

Based on this study, SSF was chosen as a lubricant at 2.25% concentration as it gave optimum hardness value with low disintegration time and wetting time. Owing to the low disintegrating property of Aerosil 200 it high loading did not promote the disintegration and wetting time[26-28]

Conclusion

To obtain FDT with sufficient hardness and DT, we evaluated the effect of the type of lubricant on the characteristics. The FDT were produced by direct compression method. The type and amount of lubricant had an influence on characteristics of FDT especially WT, DT, contact angle, SFE. Mg-St was well known as a high hydrophobic lubricant and that sodium stearyl fumarate (SSF) is less hydrophobic than Mg-St. Therefore, the DT and WT of tablets containing Mg-St increased as the amount of Mg-st increased. However, the DT and WT of FDT were influenced not only by lubricant properties, but by hardness. The polarity of the surface tablets was remarkably decreased by increasing the amount of Mg-st which related to the WT of FDT. Therefore, the contact angle of tablets increased and SFE decreased. On the other hand, the polarity of the surface tablets was remarkably increased by increasing the amount of SSF.

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