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Review Article

An Overview of Cocoa Butter: Novel Excipients for Oral Tablets

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ABSTRACT
Cocoa butter (CB) is an essential component of chocolates, which was used up to 40% as maximum. Cocoa butter has been used as a food flavour, cosmetics, suppositories additive and various biomedical applications for a longer period. Application of cocoa products as pharmaceutical excipient expanded in recent times in pharmaceutical product development. Particularly cocoa butter's melting and lubricant activity gained attention from researchers for developing oral disintegrating tablets (ODTs) or fast melting tablets (FMTs). Fast melting tablets are oral tablets formulations without the need for chewing or swallowing it with or without water. This dosage form helps to solve the limitations of dysphagia in all populations but especially for geriatrics and paediatrics. Cocoa butter is a readily available lipid that melts at body temperature 37°C. Cocoa butter has many polymorphisms and form V cocoa butter is the preferred stable form. This review explored the application of cocoa butter in pharmaceutical tablet dosage form development and its approved patent.

Keywords: cocoa butter, excipient, orally disintegrating tablets, fast melt tablets, oral tablets

INTRODUCTION

Cocoa butter (CB) is a naturally stabilized fat that is extracted from cocoa beans of the cocoa fruit (Theobroma cacao). It is used as food flavour, cosmetics additive and food biotechnology (Wei et al., 2017; Patel et al., 2020). Cocoa butter is made of a mixture of fats that becomes solid at room temperature, but melts to liquid at human body temperature, by virtue of how chocolate melts in our mouth. It helps to prevent chocolate from turning rancid as it is resistant to oxidation. Cocoa butter has prevented or removes stretch marks gained during pregnancy or weight gain. Everybody eats CB daily, few of them are applying to their skin as well. Recently many cosmetics are prepared using CB for skin care.

High polyphenol content in cocoa has fascinated attention from nutritional and pharmacological viewpoints. It shows promising potential in antioxidant, cardioprotective, neuroprotective, and chemo-preventive properties (Andujar et al., 2012). The active ingredient theobromine in cocoa beans has a broad range of therapeutic properties like diuretic, vasodilation, muscle relaxation, anti-cancer, anti-inflammatory, anti-depressant and other beneficial effects to prevent heart diseases, improve cardiac functioning and memory. These benefits of chocolate enable it to be used in chocolate drug delivery systems with the drug(s) incorporated into the chocolate base, which is now emerging as the novel drug delivery system for paediatric patients (Mayank & Kumar, 2012; Pawar et al., 2018). Human acceptability of cocoa products depends on the wide range of chemical composition including cocoa flavour and sensory properties (Aprotosoaie et al., 2016).

Recently, the researchers are using cocoa products as a novel excipient for tablet formulation. The most common preferred route of administration of medication is the oral route due to its convenience and advantages (Homayun et al., 2019). However, over the decade, there have been issues of difficulty in swallowing large tablets, especially for geriatric and paediatric patients. Hence, they do not comply with their medication, resulting in elevated incidence of ineffective therapy. Therefore, to overcome this limitation, oral disintegrating e tablets (ODTs) drug delivery system was developed.

ODTs was represented by many names, including oral disintegrating tablets, oral dissolving tablets, fast-dissolving tablets, and bite-dispersible tablets (Dey & Maiti, 2010). ODTs are defined as uncoated tablets intended to be placed in the mouth where they disperse readily within 3 mins before swallowing according to British Pharmacopoeia 2019 (British Pharmacopoeia 2019). Cocoa butter generally has a melting

point of around 34–38 °C, so it is solid at room temperature but melts readily inside the mouth (Akhter et al., 2016). It is presumed that the fast melting nature of cocoa butter will assist a fast melting tablets (FMTs) to melt and dissolve faster, therefore, it is termed as FMTs.

Cocoa butter polymorphism is one of the niche areas to be explored for the development of novel dosage forms for geriatrics and paediatrics. The plethora of research articles available about the cocoa butter tempering in chocolate melting. On the contrary, very few studies available related to the use of cocoa butter in the formulation of dosage forms. Formulations researches are oriented towards safe and effective, palatable delivery systems for drug molecules. FMTs are one of the novel dosage forms. Application of cocoa butter in the development of novel oral dosages form is the need of the hour. This present review focuses on the application of cocoa butter in FMTs.

POLYMORPHISM OF COCOA BUTTER

Cocoa butter has many polymorphisms ranging from the form I to VI with different melting points. The most common nomenclature for cocoa butter polymorphism is the Wille and Lutton nomenclature (Table 1). According to the nomenclature, form VI is the most stable form with a melting point of around 36°C and the least stable form is form I with a melting point of 16-18°C. However, form V cocoa butter is the more preferred form since it is also stable with an additional advantage of having a shiny and smooth texture that is more appealing from appearance. Other than that, form V cocoa butter will melt more quickly in the mouth than form VI cocoa butter as it has a lower melting point. Form V cocoa butter generally pre crystallized by the process called tempering. However, it will slowly be developed into form VI over time with increasing melting point and stability. Form VI cannot be made on its own but slowly developed from form V. Wile and Lutton, the conversion from form V to VI occurred very slowly when the form V cocoa butter is kept at 21°C but accelerated at higher temperatures. Hence, fast melt tablets that consist form V cocoa butter may need to be stored in a temperature of less than 21°C to slow down the conversion to form VI or a further study is needed to find the way to prevent the conversion of form V cocoa butter to form VI (Wille & Lutton, 1966; Talbot, 1994).

Table 1: Melting Points of each Cocoa Butter Polymorphism Form from Wille and Lutton Nomenclature

Polymorphism Form	Melting Points (°C)
I	17.3
II	13.3
III	25.5
IV	27.3
V	33.8
VI	36.3

COCOA BUTTER FOR ORAL TABLETS

Fast Dispersible Freeze Casted Cocoa Tablets

Nguyen and Ulrich have investigated the development of fast melt tablets (FMTs) using cocoa powder and sucrose as excipients using the freeze casting process without any active excipients. A fast dispersal cocoa tablet with a dispersal time of less than 1 min, a tensile strength of 0.14 Nmm^{-1} and crushing force of higher than 34.5N were produced, meeting the standard requirements of an FMTs. Increasing cocoa butter content resulted in increasing dispersal time. Their findings also found that sucrose can enhance the mechanical property of the FMTs as with increasing sugar content resulted in increasing crushing strength (Nguyen & Ulrich, 2014).

Co-Processed Cocoa Butter Tablet as Potential Lubricant for Paracetamol Tablets

Adeagbo, and Alebiowu have compared the lubricant activity of two formulations. One is a cocoa butter tablet with magnesium stearate and talc formulation, which is cocoa butter co-processed with magnesium stearate plus talc (CMT) and another one is a standard tablet formulation of just magnesium stearate and talc (MT). The researcher aim was not to produce fast melt tablets (FMTs) but just to study the lubricating property of cocoa butter. Their results have shown that CMT tablets have lower porosity than MT tablets. This may suggest that CMT tablets may have slower disintegration time than MT tablets alone as higher porosity of tablets promotes faster disintegration time (Adeagbo & Alebiowu, 2008).
Their study findings suggested that cocoa butter can be an effective lubricant that can help reduce lamination and capping, which are disadvantages of a direct compressed tablet. However, cocoa butter does not assist in increasing the bonding strength of the paracetamol tablets. Therefore, the addition of a binder may be required to increase the bonding strength and the mechanical strength of a cocoa butter base tablet.

Disintegrant Properties of Paracetamol Co-Processed Cocoa Butter Tablets

Alebiowu and Adeagbo used prepared paracetamol tablets with cocoa butter, which was lubricated with distinct excipient and combination of magnesium stearate and talc (CMT) to compare the disintegration time (DT) and crushing strength

friability/time of disintegration ratio (CSFR/DT) (Alebiowu & Adeagbo, 2009). From this study, the CMT tablets have longer disintegration time (DT) than MT tablets. Furthermore, with increasing cocoa butter concentration, the relative density increases accompanied by decreasing in porosity resulting in longer disintegration time. It is also observed that CSFR/DT for CMT tablets is lower than MT tablets. The crushing strength of the tablets increases with increasing lubricant concentration. From the results of this study, the combination of CMT may not be the right combination of fast disintegrating property. Therefore, other combinations of excipients with cocoa butter needs to be studied to improve the disintegration time.

Effect of Disintegrants on the Physical Properties of Fusion Moulded Cocoa Butter Based Fast Melt Tablets

Researchers investigated the effect of disintegrants on the physical properties of cocoa butter based FMTs developed by a fusion moulding method without the addition of active excipients. The study has included four different disintegrants (starch, microcrystalline cellulose, MCC and sodium starch glycollate) at 10%, 20%, and 30% concentration. Their study found that the formulation contains MCC 30% was optimized, having a disintegration time of 103 secs, hardness of 13 N and friability of 0.16%. Furthermore, it is observed that with increasing disintegrants concentration, the faster the disintegration time and increase the hardness of the FMTs (Nurul et al., 2019)

Preparation of Rebamipide Orally Disintegrating Tablets with Cocoa Powder (ODTs) (Rebamipide Chocolet)

Takano H et al., prepared ODTs of rebamipide (rebamipide chocolet) using cocoa powder with combination of sweetener (0, 2.5, 5%), which was evaluated for clinical palatability as well. The bitterness, sweetness, scent, and overall palatability of the ODTs were evaluated using 100-mm visual analog scale (VAS). Technique of direct compression was used to achieve a tablet hardness of about 50 N for the ODTs which had a hardness of 49.0 to 58.2 N and an in vitro disintegration time of 15.3 to 26.6 s. It was shown that the in vitro disintegration times were within the target time of 30 s and showed an increasing trend with an increase in the amount of cocoa powder. The in vitro dissolution behaviour of rebamipide in test solutions of pH 5.5 and pH 6.8 was almost the same as that of the commercial product, there is no difference in the dissolution properties between both of the products. The VAS scores for overall palatability from lower to higher concentration of cocoa powder significantly improved compared to that of ODT without cocoa powder. This study revealed that cocoa powder can act as a masking agent to prepare a bitter drugs ODTs of like rebamipide (Takano et al., 2019).

Palatable medicated chocolate of salbutamol and ambroxol for pediatric care (Chocolate base delivery for Pediatric)

Recently the researchers developed a palatable medicated chocolate to deliver salbutamol and ambroxol for pediatric care. The prepared combination tablets were achieved 85% in-vitro drug release, which fulfilled the FDA requirement for tablet formulation. During the stability studies analysis, no changes in physical and chemical properties for the formulated medicated chocolate. The chocolate-based formulation was stable, good therapeutic effect with high preference (Gayathri et al. 2020).

PATENT REVIEW

In the development of oral tablet formulation, patent inputs were found from the database and the approved patent for the use of cocoa butter as an excipient for oral dosage forms are listed in Table 2.

Table 2: Patent Review on Using Cocoa Butter as an Excipient for Oral Dosage Form

Patent number and Year of patent granted	Formulation	Role of Cocoa Butter	Reference
US 2003/0087937 A1-2003	Nicotine-replacement therapy	They patented nicotine-containing pharmaceutical composition comprising cocoa powder as taste masking, diluent, filler, smoothening and flavouring agent whereas cocoa butter is an alternative.	(Lindberg, 2000)
US 6,733,781 B2-2004	Fast Melt Tablets	They patented that the composition of fast melt tablets (FMTs) should have one or more low melting point compounds for example cocoa butter for the FMTs to melt at 37°C.	(Abu-Izza et al., 2004)
WO 2004/084865 A1-2004	Oral dosage form	They patented that an oral dosage form comprising of one or more active pharmaceutical ingredients, characterized	(Lindberg et al., 2004)

		in that it comprises cocoa powder and further comprises of one or more lipid ingredients including cocoa butter and cocoa butter alternatives for rapid oral uptake (sublingual/buccal uptake) and taste masking for badly tasting ingredients.	
WO 2013/044356 A9-2013	Immediate release tablets /capsules	They patented the use of cocoa butter as an excipient for dispersing vitamin D which is released immediately after the tablet or capsule disintegrates because the cocoa butter melts in the body.	(Wang & Sun,
US 2006/0057207 A1-2006	Fast Melt Tablets	They patented the composition of fast disintegrating Varenicline should include at least one lipid binder such as cocoa butter with a salivating agent, a diluent, a sweetener, a disintegrant, flavouring and a film coating agent.	(Ziegler & Johnson, 2006)

FUTURE PERSPECTIVE

There will be gestures on cocoa butter polymorphism and its melting properties in the application of formulation development, primarily oral tablets formulation. Cocoa butter base ODTs formulation with the right excipients or additives is needed to be discovered and developed with a more simple and effective method. Since cocoa butter is an easily available, cheaper and a natural source which is beneficial for human's health, so it would provoke formulation researchers' interest in this field. There are very few studies on the usage of cocoa butter to produce oral dispersible tablets, in which few studies show promising results of cocoa butter as a base. There is a need for more research to explore the potential use of cocoa butter as an excipient in the development of oral tablet formulation.

Executive summary

Cocoa Butter in Oral Tablets dosage forms

- There are many polymorphisms of cocoa butter, and the right form (form V) is stable and more suitable for formulation development.
- Very few studies on utilizing cocoa butter as an excipient in oral tablet formulations, mainly orally disintegrating tablets (ODTs) or fast melt tablets (FMTs are found.
- Some of these studies showed successful outcomes in including cocoa butter in oral tablets formulation while some observed cocoa butter is useful as a lubricant in oral tablets formulation.
- Chocolate based drug delivery may improve patient compliance as it can be used easily by pediatric patients with high preference.
- Most of the patents has patented cocoa butter as a substance that helps rapid uptake and fast release of the active ingredients.
- An optimized cocoa butter base FMTs formulation with the right excipients or additives is needed to be discovered and developed with a more simple and effective method.

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