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Formulation Development and Evaluation of Chewable Tablets as Vitamin C Placebo

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Introduction

The demand for chewable tablets has been increasing from the last decade, particularly in geriatric and pediatric due to high patient compliance[1]. This also includes patient with some sort of disability in swallowing such as neuromotor deficiency in Down syndrome individuals. Several factors contribute to the high demand on chewable tablets include suitability of dosage form in administration for kids and elderly and pleasant taste. Besides, travelling patients who may not have ready access to water are also most need of easy swallowing dosage forms like chewable tablet.

Chewable tablets are required to be broken and chewed in between teeth before ingestion[2]. Therefore, chewable tablets have a smooth texture upon disintegration, pleasant tasting and without bitter or unpleasant taste[3]. Sweeteners, both naturally occurring and synthetic are one type of functional excipient commonly used in chewable tablet formulations to mask the unpleasant taste and facilitate pediatric dosing. Ideally upon chewing, they are broken down in the mouth and ingredients are release in the process. This will require less lag time for the disintegration of tablets absorption from stomach[4].

This study was carried out to formulate chewable tablets for vitamin C placebo by developing robust formula with different excipients. The chewable tablets were prepared by using wet granulation method as it is the most commonly used granulation method. This process involves wet massing of powder blend with a granulating liquid, wet sizing and drying and finally were compressed by using tableting machine. The tablets were prepared to ensure that they are easily crushed by chewing and were evaluated for weight variation, hardness and friability.

Methods

Preparation of Granules

Sifting

Fructose, lactose, mannitol and citric acid were sifted through a 1 mm laboratory test sieve (ELE International Laboratory Test Sieve, United Kingdom).

Dry mixing

The above materials were loaded into a mixer (Kmix Kenwood, Malaysia) and were mixed for 15 minutes at high speed.

Binder preparation

i. *Preparation of starch paste:* Maize starch and FD&C orange were dissolved in a small quantity of distilled water and were stirred to dissolve completely.
ii. *Preparation of sodium carboxymethyl cellulose paste:* sodium carboxymethyl cellulose FD&C orange was dissolved in distilled water and stirred until completely dissolved.
iii. *Preparation of polyvinyl alcohol paste:* Small quantity of polyvinyl alcohol and FD&C orange were dispersed in alcohol and stirred until completely dissolved.

Granulation
The binder solution and orange flavour were added to the dry mix materials and were mixed at high speed. Then, the wet mix materials was forced through a 2.36 mm sieve (USA Standard Test Sieve, Fisher Scientific, USA) to produce wet granules.

Drying
The wet mass granules was dried in a hot air oven (Venticell MMM Einrichtungen, Germany) at different temperature (ranging from 40 to 70ºc) and time (6 hours, 12 hours, 18 hours, 24 hours and 30 hours/ more). The optimum temperature and time for drying were recorded.

Sifting and milling
The dried granules were sifted through a 1 mm laboratory test sieve (ELE International Laboratory Test Sieve, UK) to produce smaller size granules which were passed through the 1 mm mesh sieve. Then, magnesium stearate and talc powder were added into the mixture.

Compression
The mixture was compressed by using 11.5 mm standard flat circular punches with plain surfaces on both sides using a tableting machine (N.R Industries Co. Ltd, Thailand). The weight, hardness and thickness were monitored during the process.

Evaluation of tablets
The physical testing specifications for tablets, such as size, shape, colour, friability and breaking force or hardness can be a quick quality check.

Friability
Friability of tablets was determined using friabilator (Electrolab EF-2, India). Twenty tablets from each batch were selected randomly and the pre weight was measured using electronic weighing balance. Then, the tablets were placed into the friabilator and were subjected to the combined effect of abrasions and shock in friabilator for 100 revolutions. Tablets were examined if capping occurs and reweighed. The mean loss of weight was calculated and the friability was determined using the formula below:

$$Friability = \frac{Initial\ weight - Final\ weight \times 100\ \%}{Initial\ weight}$$

The tablets were considered to pass the test if the friability values are 1% or less.

Hardness
Twenty tablets from each batch were selected randomly. Hardness or tablet crushing of tablets was determined using hardness testing machine (PharmaTest, Germany).

Weight variation
Weight of 20 tablets (selected randomly) was measured using electronic weighing balance (Mettler Toledo, Switzerland) and the average values was calculated.

Results

Chewable tablets were prepared by selecting the best excipients in four trials by using wet granulation technique. Mannitol, fructose and lactose were chosen as diluents or sweeteners. Apart from this, maize starch, sodium carboxymethyl cellulose and polyvinyl alcohol were used as binders whilst citric acid was used as taste enhancer. Talc powder and magnesium stearate were used as glidant and lubricant. FD&C orange and orange flavour were used as colour and flavouring agent, respectively (Table 1). The optimum temperature and time for drying were 70ºC for 24 hours as shown in Table 2. The results of physical characteristics such as weight, friability, hardness, diameter and thickness of chewable tablets were shown in Table 3.

Table 1: Formulation of chewable tablet (composition)				
Ingredients	**Trial 1**	**Trial 2**	**Trial 3**	**Trial 4**
Mannitol	206.50	206.50	317.45	350.00
Fructose	110.00	110.00	110.00	146.20
Lactose	103.45	103.45	-	-
Maize Starch	68.75	68.75	68.75	-
Sodium carboxymethyl cellulose	-	27.50	27.50	27.50
Polyvinyl alcohol	27.50	-	-	-
Citric acid	27.50	27.50	20.00	20
Magnesium stearate	2.750	2.750	2.75	2.75
Talc powder	2.75	2.75	2.75	2.75
Distilled water	Small quantity	Small quantity	Small quantity	Small quantity
Ethyl alcohol/ ethanol	Small quantity	-	-	-
FD & C orange	0.35	0.35	0.35	0.35
Orange flavor	0.45	0.45	0.45	0.45
Tablet weight (mg)	550	550	550	550

Table 2: Effect of different drying time and temperature on the wet mass granule					
Trial	Drying Time (hour)	Drying Temperature (ºC)			
		40	50	60	70
1	6	-	-	-	-
	12	-	-	-	-
	18	-	-	-	-
	24	-	-	-	-
	More than 30	-	-	-	Dry granule
2	6	-	-	-	-
	12	-	-	-	-
	18	-	-	-	-
	24	-	-	-	-
	More than 30	-	-	-	Dry granule
3	6	-	-	-	-
	12	-	-	-	-
	18	-	-	-	-
	24	-	-	-	-
	30	-	-	-	Dry granule
4	6	-	-	-	-
	12	-	-	-	-
	18	-	-	-	-
	24	-	-	-	Dry granule

Table 3: Physical Characteristics of Chewable Tablets

Trial	Weight variation range (mg)	Friability (%)	Hardness range (Newton)	Diameter (mm)	Thickness (mm)
1	545-560	0.26	61-69	11.5 ± 0.06	4.29 ± 0.03
2	548-559	0.29	68-72	11.5 ± 0.05	4.35 ± 0.04
3	547-560	0.25	70-83	11.5 ± 0.07	4.40 ± 0.02
4	548-556	0.18	75-86	11.5 ± 0.05	4.38 ± 0.03

Discussion & Conclusion

This study was conducted to formulate and evaluate the chewable tablets as vitamin C placebo and it was prepared by using wet granulation method. Different excipients were used to find the best formulation to prepare chewable tablets. The physical characteristics such as weight, friability, hardness, diameter and thickness were evaluated for each batch of trial.

From the results obtained, the expicients of Trial 4 with 70ºC drying temperature for 24 hours were found to be a simple and robust method to prepare chewable tablets as compared to Trial 1, 2 and 3. There were a few factors of such selection and this include drying time of wet granules for Trial 4 at 24 hours as compared to Trial 1, 2 and 3 which needed longer time to dry (≥30 hours). Besides, drying temperature used to dry the wet granules of Trial 4 excipients were 70ºC and we did not increase the temperature as one of the excipient, fructose has a lower melting point as compared to other sugars[5]. The drying temperature of 60ºC was used in a study of Patil and colleagues[4] who worked on the development of the formulation and evaluation of chewable tablets containing non-sedative histamine. In addition, granules for Trial 1, 2 and 3 were found over wetted and required considerable pressure to form the tablets and caused difficulty during compression.

Halal issue is another important factor in pharmaceutical products that affect Muslim consumers. Besides halal food, halal pharmaceuticals are supposed to come from halal, clean, and healthy sources because they are something which are eaten or consumed. Foods and pharmaceuticals permitted for Muslim consumption does not include intoxicants such as drugs and alcohol among others[7]. In this study, ethyl alcohol was used as one of the excipients in Trial 1 to dilute polyvinyl alcohol as a binder. Therefore, since the use of alcohol would raise a lot of concerns to many people[6], we decided not to consider the formulation even though current tolerable amount of alcohol is 0.01% in the final product for halal certification in Malaysia[7].

Hence in this study, it was concluded that the Trial 4 is the optimized vitamin C placebo formulation for chewable tablets.

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