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The Effect of Crospovidone on the Dissolution Profile of Amlodipine Besylate from Fast Orally Dissolving Film

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Keywords: Amlodipine besylate; Crospovidone; Solvent casting; Fast orally dissolving film

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Abstract

BACKGROUND: Fast Orally Dissolving Film preparation can be used for patients with problems in ingesting solid dosage forms, such as mentally ill, elderly, geriatric and patients who are reducing fluid intake or nausea.

AIM: This study aimed to formulate and evaluate the rapid dissolution of amlodipine besylate.

METHODS: Amlodipine besylate film was prepared by solvent casting method by using hydroxypropyl methylcellulose (HPMC) as film formers, crospovidone as superdisintegrant with Varian concentration F1 (2%), F2 (4%), F3 (6%) and F4 (8%), PEG 400 as plasticizer, sucralose and sorbitol as sweetener, citric acid as saliva stimulation, and grape essence as flavoring and coloring agent. Characteristics of films include organoleptic, weight uniformity, film thickness, surface pH, swelling, uniformity of content, time of disintegration, and dissolution.

RESULTS: All formulated films produced a good film, smooth, transparent and uniform physical properties. F2 with polymer HPMC and the 4% concentration of crospovidone was the best formula with 31.50 seconds of disintegration time, the index expanding at the 15 second by 242.29% and the cumulative percent of the drug at 80 seconds by 98.08%.

CONCLUSION: Amlodipine besylate can be formulated into fast orally dissolving film preparations using HPMC and crospovidone polymers so that they may be considered for use in the treatment of hypertension for patients with drug-induced problems in tablet or capsule form.

Introduction

Recently, fast dissolving films are gaining interest as an alternative to fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides a marketing advantage and increased patient compliance. As the drug is directly absorbed into systemic circulation, degradation in the gastrointestinal tract and first pass effect can be avoided [1].

Fast dissolving drug delivery systems were first invented in the late 1970s as to overcome swallowing difficulties associated with tablets and capsules for pediatric and geriatric patients. Buccal drug delivery has lately become an important route of drug administration. Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal delivery, also known as orally dissolving films [1]. Bioavailability of the drug will be enhanced due to high blood flow since the permeability of oral mucosa is 4-1000 times greater than that of skin [2].

Thin films have shown the capabilities to improve the onset of drug action, reduce the dose frequency and enhance the drug efficacy [3]. These points make this formulation most popular and acceptable among pediatric and geriatric patients and patients with fear of choking [1].

Advantages over conventional dosage forms

A thin film dissolves faster than other conventional dosage forms. Thin films are less friable and easy to carry dosage form compared to commercialized orally fast disintegrating tablets, which need special packing. Likewise, a single dose of the strip can be carried individually without requiring the secondary container. It is very important to pay attention the poor stability of liquid dosage forms, especially the aqueous formulations. Unlike the thin films, there is a need for great care during accurate measurement of the amount and shaking the bottle every time before administration may contribute to less acceptance by the patients [4].

Amlodipine is a calcium channel blocker used in the management of hypertension and angina pectoris. It is long-acting with effects similar to nifedipine. Administered orally, the drug is well absorbed and peak blood concentration is reached after 6-12 h. Plasma elimination is biphasic and terminal elimination half-life is about 30-50 h. The absolute bioavailability of between 60 and 65% has been estimated [4].

Amlodipine is a calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells [5].

Material and Methods

The materials used in this research are amlodipine besylate (Unichem Laboratory, Ltd), PEG 400 (Brataco), sorbitol, sucralose, citric acid, HPMC (Wuhan Senwayer Century Chemical Co., Ltd.), crospovidone (Huangshan Bonsun Pharmaceuticals Co., Ltd.), sodium hydroxide (Merck), ascorbic acid (Merck) and distilled Water (Brataco).

The ODF preparation was prepared by using HPMC and crospovidone polymers by solvent casting method. All materials were weighed. A number of film-forming polymer solutions were developed in distilled water for 15 minutes. An amount of sorbitol and sucralose were dissolved in 5 ml of distilled water and then added citric acid. The solution was stirred until completely dissolved then added PEG 400, crospovidone and tween 80 and grape essence added with constant stirring for 45 min. The solution mixture was allowed to stand at room temperature to remove air bubbles. The film solution was poured into a 9x10 cm mold and then dried for 24 hours. After drying, the film was removed from the mold then cut to 2x3 cm so that each film contains 5 mg of amlodipine besylate. The formula can be seen in Table 1.

Table 1: The formulation of fast orally dissolving films

Material (mg)	Formula			
	F1	F2	F3	F4
Amlodipine besylayte	75	75	75	75
HPMC	250	250	250	250
Crospovidone (% w/w)	2	4	6	8
PEG 400	40	40	40	40
Citric acid	35	35	35	35
Tween 80	q.s	q.s	q.s	q.s
Sorbitol	30	30	30	30
Sucralose	20	20	20	20
Grape essence	q.s.	q.s.	q.s.	q.s.
Distilled water	15	15	15	15

Note: q.s. = *quantum satis* = sufficiently.

The organoleptic characteristics of the amlodipine besylate ODF preparations observed included homogeneity, color, odor, and texture visually seen by 10 panelists.

For the evaluation of the weight of the film, six sheets of each formula were taken and weighed one by one and then determined the standard deviation. The film thickness was measured in the middle and the four corners. The average film thickness value was calculated and the standard deviation should be less than 5%. For the evaluation of the pH of the preparation, a film was dissolved in 10 ml of distilled water in the container and the pH of the preparation was measured using a pH meter. Measurements were made of three films of each formula.

Uniformity of amlodipine besylate content was determined by dissolving one sheet of film with phosphate buffer pH 6.8 in a 100 ml measuring flask, 1 ml of solution was then diluted with phosphate buffer pH 6.8 to 10 ml. Amlodipine besylate levels were determined by spectrophotometer at a wavelength of 364 nm. Measurements were made of three films of each formula.

Disintegration time of the film was performed by using the basket then the apparatus with a phosphate buffer solution medium of pH 6.8 at 37 ± 0.5°C isintegration time was observed in each film. The film preparation was called destroyed when there was no more film left in the basket. Measurements were made of six films per formula [6].

The film was allowed to expand in 15 ml of phosphate buffer medium pH 6.8 in a petri dish. The film was taken from a petri dish and removed with filter paper then the film was weighed. Index swelling was calculated by the following equation [7]:

$$\text{Index swelling (\%)} = \frac{wt - wo}{wo} \times 100\%$$

Description:

wt: the weight at certain time t

wo: the weight at time 0

Dissolution test was carried out with a paddle type dissolution apparatus, rotating speed 50 rpm, the dissolution medium of phosphate buffer pH 6.8 was 900 ml at a temperature of 37 ± 0.5°C. A film was inserted into the dissolution device. Solution was taken as much as 2 mL at the 20^{th}, 40^{th}, 60^{th}, 80^{th}, 100^{th}, and 120^{th} seconds. Uptake the solution was calculated at the maximum wavelength [8].

Results

Organoleptic evaluation was one of the important things to be observed because ODF preparations directly came into contact with the oral cavity. The resulting ODF preparations must have a taste that was acceptable to many people. The use of HPMC polymers produced smooth, non-sticky and transparent film surfaces in all four formulas (Figrue 1).

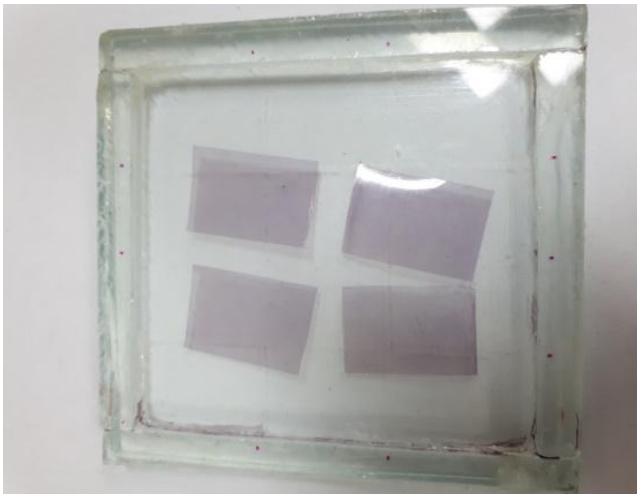

Figure 1: The amlodipine besylate fast orally dissolving films

Measurement of the uniformity of weight and thickness in the film was necessary because it was directly related to the amount of drug in the film. The ideal film thickness should be in the range of 50 to 1000 µm [3].

Table 2: Result of weight uniformity test and film thickness of amlodipine besylate fast orally dissolving films.

Formula	Weight (mg)	Thickness (mm)
F1	45.33 ± 0.516	0.057 ± 0.0009
F2	45.50 ± 0.547	0.054 ± 0.0003
F3	45.58 ± 0.376	0.056 ± 0.0008
F4	45.61 ± 0.377	0.052 ± 0.0011

Note: F1 = ODF with crospovidone 2%; F2 = ODF with crospovidone 4%; F3 = ODF with crospovidone 6%; F4 = ODF with crospovidone 8%.

In Table 2, we can see that the ODF F1 had a weight of 45.33 ± 0.516 mm, F2 of 45.50 ± 0.547 mm, F3 of 45.58 ± 0.376 mm and F4 of 45.61 ± 0.377 mm. Based on the above results, it could be seen that there was little difference in the weight of the film on each formula, but still could be categorized quite uniformly. In the film thickness test results, F1 had a thickness of 0.057 ± 0.0009 mm, F2 of 0.054 ± 0.0003 mm, F3 of 0.056 ± 0.0008 mm and F4 of 0.052 ± 0.0011 mm.

Determination of the surface pH of the film aimed to ensure no oral mucosal side effects because too acidic or alkaline pH could cause oral mucosal irritation. Surface pH should be neutral or near neutral [6]. In Table 3 it can be seen that the film preparation of the four formulas had a neutral pH of 6.73-6.83, so irritation to the oral mucosa could be avoided [9].

In Table 3 we can be see that the levels of drug obtained ranged between 97.80% and 99.46%. The uniformity limit of the content was 85%-115% with the standard deviation should be less or equal to 6% [10]. The content uniformity test was performed to ensure that all films contained a number ingredient of the desired drug. The uniformity of the content was determined by estimating the active ingredient content of the drug present in each film [8]. The result of surface pH test, and drug content in the film can be seen in Table 3.

Table 3: Result of surface pH test, disintegration time, and drug content in the amlodipine besylate fast orally dissolving films

Formula	pH	Drug levels (%)	Disintegration time (sec)
F1	6.77 ± 0.058	98.16 ± 0.178	34.66 ± 2.943
F2	6.83 ± 0.058	99.46 ± 0.294	31.50 ± 2.880
F3	6.80 ± 0.100	97.80 ± 0.355	39.00 ± 1.483
F4	6.73 ± 0.058	98.28 ± 0.459	40.83 ± 1.602

Note: F1 = ODF with crospovidone 2%; F2 = ODF with crospovidone 4%; F3 = ODF with crospovidone 6%; F4 = ODF with crospovidone 8%.

Drug components are fully available for absorption digestive tract; therefore, the preparation must be destroyed for release the drug into body fluids to dissolve [11]. Disintegration time is expected to provide an overview of preparation time ODF is experiencing disintegration. In Table 3, the fastest disintegration time was generated by F1 compared to other formulas, then followed by F2, F3, and F4.

The swelling nature of the film was usually due to the role of the polymer which increased the hydrophilicity. In many cases, inflated index rates play an important role in controlling drug release [3]. The film swelling test was carried out to see the magnitude of the increased film mass allowed to expand in the phosphor buffer solution of pH 6.8 for 20 seconds. The increase in mass of the film indicated an increase in the hydration of the film. The more water was absorbed, the power of swelling was better from the film [12]. The swelling index of the formulas can be seen in Table 4.

Table 4: The swelling index of the amlodipine besylate fast orally dissolving films

Formula	Time (sec)	Swelling index (%)
F1	5	81.98 ± 1.186
	10	152.73 ± 2.357
	15	231.42 ± 4.899
	20	-
F2	5	96.76 ± 1.070
	10	174.93 ± 1.394
	15	242.29 ± 1.922
	20	-
F3	5	74.70 ± 1.159
	10	136.40 ± 1.445
	15	206.93 ± 3.382
	20	239.34 ± 1.213
F4	5	67.27 ± 1.538
	10	128.49 ± 0.514
	15	170.91 ± 0.214
	20	233.54 ± 4.575

Note: F1 = ODF with crospovidone 2%; F2 = ODF with crospovidone 4%; F3 = ODF with crospovidone 6%; F4 = ODF with crospovidone 8%.

The sequence of swelling index percentage was as follows F2 > F1 > F3 > F4. In F1 and F2, at the 15th second, F1 produced an swelling index of 231.42 ± 4.899% and F2 produced an swelling index of 242.29 ± 1.922% while in the 20 seconds, F1 and F2 were not taken into account again because at the time some of the films have been destroyed so that the film was no longer intact and the final weight of the film could not be weighed again. This could be attributed to the effect of crospovidone that helps speed up the film's swelling. The effects of crospovidone as superdisintegrant were based primarily on the ability to swell without forming the gel so that in the presence of crospovidone could accelerate the water absorption in the film [13]. In F3 and F4, the swelling index was calculated up to the 20 seconds, F3 produced a swelling index of 239.34 ± 1.213% and F4 produced a swelling index of 233.54 ± 4.575%.

Dissolution test using paddle method and phosphate buffer pH 6.8 as dissolution medium. The parameter for stating the dissolution rate is percent cumulative, which is the percentage of amlodipine which is released from the Fast ODF dosage form at interval of 20, 40, 60, 80, 100 and 120 seconds with crospovidone concentration varied 2%, 4%, 6% and 8%. The fastest dissolution rate was shown by F2 > F1 > F3 > F4. This was due to variations of the crospovidone concentration used in the formula. The results of statistical analysis showed that usage crospovidone with a concentration of 4% showed the most drug release many and in the shortest time. Cumulative percent yield F1 to powder exposure from seconds 0 to seconds 120 can be seen in Table 5. Crospovidone quickly wetted into the film by saliva resulting in an expansion of volume and hydrostatic pressure that occurs rapid disintegration [12].

Table 5: Cumulative percent average

No.	Time (sec)	% cumulative F1	% cumulative F2	% cumulative F3	% cumulative F4	% cumulative Crospovidone powder
1	20	18.09	26.28	16.47	15.93	47.61
2	40	39.68	48.17	38.05	36.46	71.06
3	60	65.22	71.63	63.93	62.87	98.31
4	80	83.62	98.08	83.43	83.67	99.22
5	100	100.03	100.62	93.72	91.68	99.87
6	120	101.70	101.71	98.93	97.97	101.90

Note: F1 = ODF with crospovidone 2%; F2 = ODF with crospovidone 4%; F3 = ODF with crospovidone 6%; F4 = ODF with crospovidone 8%.

The amount of amlodipine besylate concentration dissolved in the medium from 0 – 120 seconds were calculated based on the area under curve (AUC). Results AUC_{0-120} calculation can be seen in Table 6. AUC calculation results showed that the amlodipine concentration dissolved in the medium from 0 – 120 seconds with 2%, 4%, 6% and 8% variations of crossover one concentration. Drug given orally in solid dosage form; the bioavailability can be varied from zero to 100%. AUC is an important parameter in describing the amount of drug in the body.

The results of the AUC calculation showed that the amlodipine concentration dissolved in the medium from 0 to 120 seconds was greater in the formula last crospovidone powder comparator for F1 to F4, F2 using 4% crospovidone concentration had the largest AUC then followed by crospovidone concentration of 2%, then crospovidone 6% and the last 8%.

Table 6: Results of AUC calculations

Formula	AUC (mcg/ml)
Crospovidone powder	9342.46
F1	7150.06
F2	7912.76
F3	6921.46
F4	6798.53

Discussion

Crospovidone was effectively used on low concentration of 2-4% [8]. Unlike other superdisintegrants, which rely primarily swelling for disintegration, crospovidone uses a combination effect swelling and wicking so that ODF preparations can release drug ingredients from the dosage form quickly [14].

The conclusion of this research is amlodipine besylate can be formulated into fast orally dissolving film preparation using HPMC polymer with crospovidone. A variation concentration of crospovidone gives effect to characterization of amlodipine besylate fast orally dissolving films. F2 with 4% crospovidone concentration is the best formula with 31.50 seconds disintegration time, swelling index at 15 seconds by 242.29% and percent cumulative drug in the 80th second of 98.08%.

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