Drug Release from Acetaminophen Strip

การปลดปล่อยยาจากสทริพอะเซตามิโนเฟน

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ABSTRACT

The aim of this study was to formulate an acetaminophen strip by using the solvent casting method. Strip formulation contained acetaminophen, HPMC E5 and xylitol. It was found that acetaminophen was solubilized or distributed in the polymer. The amount of drug and polymer were shown to have an effect on mechanical properties of the strips. Xylitol is important for peelability of strip. Formulation containing xylitol showed percent cumulative drug release greater than 85% within the first 5 minutes.

บทคัดย่อ

การศึกษานี้ได้ พัฒนา อะเซตามิโนเฟนสทริพชนิดละลายในปาก โดยใช้เทคนิคการเทฟิล์มแบบ โซลเวนท์ แคสทิง ตำรับยาประกอบด้วยตัวยาอะเซตามิโนเฟน, เอชพีเอ็มซีอี 5 และไซลิทอล ผลการประเมินคุณสมบัติทางเคมีและกายภาพของแผ่นฟิล์มพบว่าตัวยามีการละลาย หรือกระจายตัวอยู่ในสารก่อฟิล์ม ปัจจัยที่มีผลต่อคุณสมบัติทางกายภาพของยาคือ ปริมาณยาและสารก่อฟิล์ม ไซลิทอลมีความสำคัญต่อความสามารถในการลอกออกจากเพลท ตำรับที่ใส่ไซลิทอล สามารถละลายและปลดปล่อยยาได้ มากกว่า 85% ภายใน 5 นาทีแรก

Key Words: Orodispersible strip, Acetaminophen strip, Solvent casting

คำสำคัญ: สทริพชนิดละลายในปาก อะเซตามิโนเฟนสทริพ โซลเวนท์ แคสทิง

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Introduction

Recently, orally dissolving strips are gaining interest as an alternative of fast dissolving tablets (Bala et al., 2013). These thin films or strips are convenient, not only for patients with dysphagia, a fear of choking, swallowing difficulties, but also to the general population (Buck et al., 2013). Orodispersible film (ODF) can be found in the different terms, for example, wafer, oral film, thin strip, orally dissolving film, flash release wafer, quick dissolve film (Hoffman et al., 2011). The official term defined by the European Medicines Agency is orodispersible film (ODF) (Hoffman et al., 2011). ODF or strip that composes of a water dissolving polymer can quickly hydrate by saliva, adhere to mucosa and disintegrate within a few seconds, dissolve and releases medication for oromucosal absorption or maintain the quick-dissolving aspects for gastrointestinal absorption (Arya et al., 2010; Nagaraju et al., 2013; Pathare et al., 2013; Preis et al ., 2014). Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/ capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral strip (OS) (Dixit et al., 2009). OS are gaining interest because of its advantages :

- Rapid disintegrate
- Fast dissolving
- Better patient compliance
- Avoid the first – pass metabolism
- Ease of swallowing and no risk of choking

(Arya et al., 2010; Bala et al., 2013)

Manufacturing of ODFs is based mainly on established technologies such as tablet coating, solvent casting or hotmelt extrusion (Arya et al., 2010; Hoffman et al., 2011).

Objective of the study

The aim of this study was to prepare and evaluate fast dissolving oral strip of acetaminophen using HPMC E5, and to study the effect of two formulation factors on the drug release. Strips were prepared by casting method and acetaminophen was used as a model drug.

Methodology

Strip preparation

Four formulations of the strips were prepared according to Table 1. Xylitol in each formulation (0.5% w/w) was dissolved in deionized water at a ratio of 1:4 by weight and stirred until clear solution was obtained (Solution A). The remaining deionized water was maintained at the temperature of 80^{o}C. Acetaminophen (1 or 4 %w/w of total weight) was added into hot deionized water. The solution was maintained at the temperature of 80^{o}C (Boateng et al., 2009). Then HPMC E5 was dispersed into the hot acetaminophen solution. The solution was continuously stirred with a magnetic stirrer until clear solution was formed (Solution B). The solution A was added into the solution B. Then the mixture was stirred and cooled for 30 minutes. The mixture was left until the air bubbles disappeared. Each film sample was prepared by pouring 10 g of the gel mixture into glass petri dish (diameter 8.7 cm) and left to dry in oven at 50^{o}C for 24 hours.

Table 1 Composition of the strip formulation

Formulation	HPMC E5 (%w/w)	Acetaminophen (%w/w)	Xylitol (%w/w)
A	5	1	-
B	5	4	-
C	5	1	0.5
D	5	4	0.5

Physical appearance

Strip appearance was evaluated by visual inspection.

Fourier transform infrared (FTIR) spectroscopy

Each of the component (acetaminophen, HPMC E5, xylitol) or formulations A-D were ground and mixed with KBr. Sample-KBr disk was prepared by compression at a compression force of 1 ton. All samples were analyzed between 4000 and 400 cm^{-1} (FT-IR: Nicolet 6700, Thermo Scientific, U.S.A.).

Tensile properties

The texture analyzer (TA.XT. plus Texture analyzer, Stable Micro Systems, England) was calibrated. The measurement was performed using a 5 kg load cell, a gauge length of 3 cm and a test speed of 2 mm/s. The 1 cm x 5 cm strip was held between two clamps positioned at a distance of 3 cm. The strips were pulled by the top clamp at the rate of 2 mm/s. The test was concluded at the film break. Tensile strength (TS), percentage elongation (E) and Young's modulus (YM) were computed to evaluate the tensile properties of the films. The average and standard deviation for ten samples were recorded.

Drug content in strip

Acetaminophen content in the polymer strip was analyzed by using spectrophotometer. The strip was cut into 2.5 x 4.8 cm square strips and accurately weighed. The sample was dissolved in water and was appropriately diluted before measuring the absorbance value. The absorbance value was measured at the wavelength of 243 nm. Three replicate samples were measured.

Drug release study

Strip was cut into 2.5 cm x 4.8 cm square strips. The dissolution studies were performed according to USP 36 (Apparatus 2). The strip was placed between the stainless sieve (12 mesh, 80 mm diameter) to prevent the film from floating, as shown in Figure 1. The paddle rotation speed was adjusted to 50 rpm in 900 mL of simulated saliva. Samples (10 mL) were withdrawn at 30 second, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 40, 50 and 60 minute time interval. Replace the aliquots withdrawn for the analysis with equal volumes of medium at the same temperature. Each sample was diluted and the amount of drug dissolved in the sample was determined by using spectrophotometer at a wavelength of 243 nm. The dissolution test was studied at 37±0.5 ^{o}C.

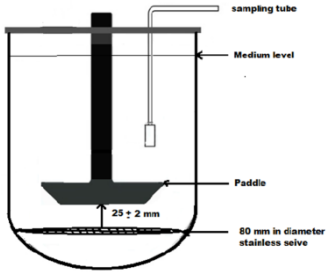

Figure 1 Apparatus used in dissolution study

Results

Strips containing 1% w/w drug (Formulation C) were initially transparent but became opaque after storage, while strips with 4% w/w drug (Formulation D) were stiff and opaque after drying (Figure 2).

Strips without xylitol (A and B) could not be peeled from petri dish.

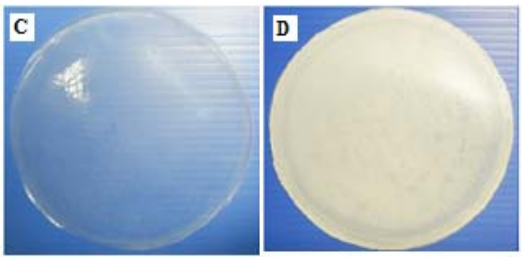

Figure 2 The physical appearance of the formulations

The absorption bands appeared in the fingerprint at > 1500 cm^{-1} are usually used for the analysis, while the band <1500 cm^{-1} are very complex and it is difficult to be confident in the assignment of absorptions to particular functional groups. Thus the interpretation is focused on the bands > 1500 cm^{-1}. The major absorptions which can be observed in acetaminophen molecule and HPMC E5 have been shown in Tables 2-3. The acetaminophen used in this study presents the main absorption bands at 3325.92 cm^{-1}, 3162.30 cm^{-1}, 1877.24 cm^{-1}, 1652.35 cm^{-1}, 1610.39 cm^{-1}, 1564.15 cm^{-1}, 1505.88 cm^{-1} and 808.47 cm^{-1}(Figure 3). The major absorption bands of HPMC E5 used in this study showed the main absorption bands at 3482.19 cm^{-1}, 2934.76 cm^{-1}, 1653.46 cm^{-1} and 1059.10 cm^{-1}, which correspond to the presence of O-H, C-H, C=O and C-O-C (Figure 4). Figure 5 shows the FTIR spectrum of xylitol. Formulation C (Figure 6) which contained 1% acetaminophen in 5% HPMC E5, showed only HPMC E5 peaks at 2934.60 cm^{-1} (C-H), 1653.29 cm^{-1} (C=O), 1066.90 cm^{-1} (C-O-C) and the slightly shifted peaks at 3446.03 cm^{-1}(O-H). An absence of acetaminophen peak may be due to the low drug concentration used. For formulation D (Figure 7), which contained 4% acetaminophen in 5% of HPMC E5, acetaminophen main sharp peaks at 3326.35 cm^{-1}, 3164.32 cm^{-1}, 1655.31 cm^{-1}, 1610 cm^{-1}, 1565.72 cm^{-1}, 1506.74 cm^{-1}, and 808.46 cm^{-1} and HPMC peaks at 2926.82, 1655.31 and 1066.73 cm^{-1} ,which were slightly shifted ,were shown. This suggests the absence of any interaction between the drug and the polymer.

Table 2 Infrared spectrum of acetaminophen (Qi et al., 2008)

Band	Wavenumber	Assignment
A	3360 cm^{-1}	N-H amide stretch
B	3000 cm^{-1}-3500 cm^{-1}	Phenolic OH stretch
C	3000 cm^{-1}	C-H stretching
D	1840-1940 cm^{-1}	Aromatic overtone region
E	1650 cm^{-1}	C=O amide strech
F	1608 cm^{-1}	Aromatic C=C stretch
G	1568 cm^{-1}	N-H Amide bending
H	1510 cm^{-1}	Aromatic C=C stretch
I	810 cm^{-1}	=C-H bending

Table 3 Infrared spectrum of HPMC E5 (Akinosho et al., 2013)

Wavenumber	Assignment
3500-3400 cm^{-1}	O-H stretching
2900cm^{-1}	C-H stretching
1650-1600 cm^{-1}	C=O stretching
1100-1000 cm^{-1}	C-O-C stretching

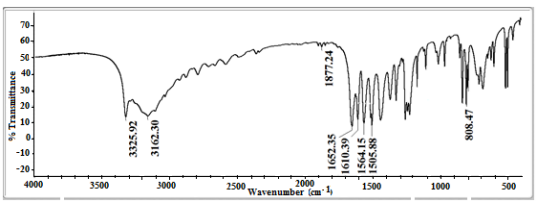

Figure 3 FTIR spectrum of acetaminophen

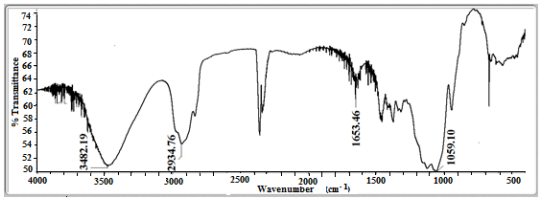

Figure 4 FTIR spectrum of HPMC E5

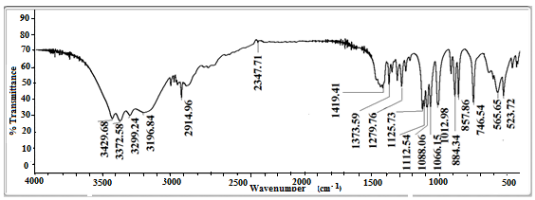

Figure 5 The FTIR spectrum of xylitol

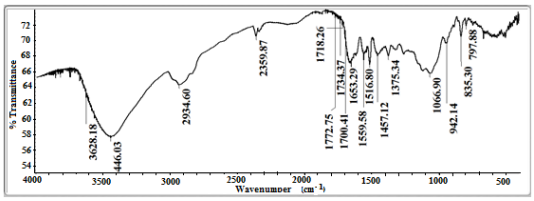

Figure 6 FTIR spectrum of Formulation C

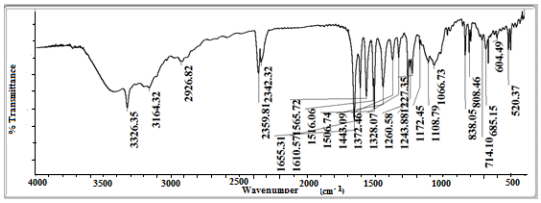

Figure 7 FTIR spectrum of Formulation D

The high tensile strength and high Young's modulus values indicated hard and brittle strips. Tensile strength and Young's modulus values have a direct impact on patient acceptance and clinical performance of the final dosage form as the risk of irritation from brittle strip may occur (Nair et al., 2013). Tensile strength, % elongation and Young' s Modulus values of four formulations were shown in Table 4.

Table 4 Tensile properties

Formula	Tensile strength (MPa) Mean±S.D.	Elongation (%) Mean±S.D.	Young' Modulus (MPa/%) Mean±S.D.
A	N/A	N/A	N/A
B	N/A	N/A	N/A
C	34.1055±4.0604	10.0364±3.0242	7.7963±1.0304
D	15.5262±2.4852	3.3534±0.5964	6.1424±0.9078

Acetaminophen contents of formulations containing 1% and 4% drug were 109.54±9.37 % and 108.79±6.32 %, respectively. The result showed that variation was obtained in both formulations (C and D).

The *in vitro* release studies were carried out in simulated saliva. The cumulative drug release profile at time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 40, 50, 60 minutes of all formulations were reported (Figure 8 and Table 5). Formulation C and D released 85% of drug within 3-5 minutes. For the first 3 minutes, there was no significant difference in the percent cumulative drug release between formulation C and D (P>0.05). After 3 minutes, the percent cumulative drug release of formulation C was higher than that of formulation D (P<0.05).

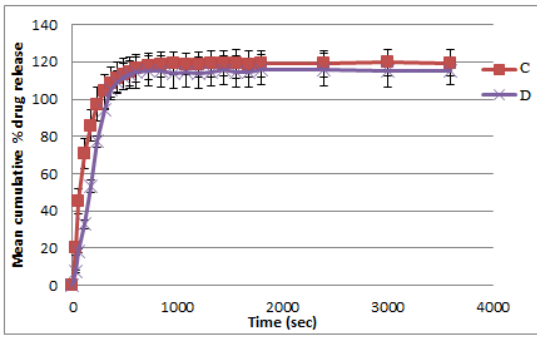

Figure 8 The cumulative drug release profile

Table 5 The percent cumulative release

Sampling time (second)	% Cumulative release			
	Formulation C		Formulation D	
	Mean	S.D.	Mean	S.D.
60	45.09	6.45	18.38	1.00
180	85.6	8.47	53.33	3.30
300	104.15	8.92	94.61	0.54
600	116.47	7.46	114.22	8.60
1800	118.93	7.23	115.60	8.03
3600	119.38	7.17	115.17	7.63

Discussion and Conclusion

Acetaminophen strip could be prepared by using simple method. The dry strips of formulation A and B could not be peeled from petri dish. It indicates that xylitol is important for peelability of strip. Formulation C showed higher tensile strength, percent elongation and Young's modulus than that of formulation D eventhough both formulations contained the same amount of polymer. It appears that the texture of strip was changed when the amount of drug was increased. For drug release study, formulations C and D showed percent cumulative drug release greater than 85% within the first 5 minutes. The percent cumulative drug release greater than 100% found at end of the study period may be due to the high variation in the drug content of the strips. From the results of our previous study, it was shown that the presence of HPMC E5 and xylitol did not interfere the drug analysis.

Acknowledgement

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