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CONTENT

Original article

Premenstrual syndrome: A cross-sectional study among women of reproductive age in Sibu, Sarawak, Malaysia

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Abstract

Background: Premenstrual syndrome (PMS) is a collection of physical and psychological symptoms in relation to the menstrual cycle. Little is known about the prevalence and attitude of pre-menstrual syndrome among women of reproductive age in Sibu, Sarawak, Malaysia.

Materials & Methods: A cross-sectional study was carried out during the first quarter of 2017. A total of 255 women of reproductive age from both urban and rural areas of Sibu were voluntarily participated and face-to-face interview was undertaken.

Results: The prevalence of PMS was 44.3% (95% CI: 38.1%, 50.6%) and more than half of the respondents (56.1%; 95% CI: 49.8%, 62.3%) had positive attitude towards PMS. Although age, ethnicity, residence and education status were found to have significant association with having positive history of PMS, none of them were significantly related to the attitude towards PMS. The common symptoms of PMS were increased appetite, acne, mood swing, irritability and breast tenderness.

Conclusion: A significant portion of women in reproductive ages had positive history of PMS.

Keywords: Premenstrual syndrome, PMS, Sibu, Malaysia

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Introduction

Premenstrual syndrome (PMS) is a collection of physical and psychological symptoms in relation to the menstrual cycle. Symptoms range from mild or moderate to severe debilitating presentations which can cause disruptions in a woman's life. The psychological symptoms of premenstrual syndrome consist of affective lability (e.g mood swings), apathy, confusion, insomnia, anxiety, depressive symptoms, feeling of uselessness and marked irritability. The somatic presentations of PMS include fatigue, headache, loss of appetite, abdominal bloating, breast tenderness and acne. Most women suffer from at least one symptom of premenstrual syndrome and it usually does not affect their daily activities enormously.[1,2] Various studies revealed varying prevalence of PMS in different countries and settings.[3-7] The prevalence of PMS ranges from 12.2% in France[5] to 74.6% among secondary students in Seremban, Malaysia.[3] Besides, a study carried out in France showed 79.8% of symptomatic women with premenstrual syndrome did not seek medical consultation as they assumed symptoms were normal, 18.7% of symptomatic women sought treatment and 1.59% of symptomatic women were unsure.[8]

Little is known about the prevalence and attitude towards PMS among women of reproductive age in Sibu, Sarawak, Malaysia. Therefore, the present study was undertaken.

Aim:

To study the prevalence and attitude towards premenstrual syndrome among women of reproductive ages in Sibu, Sarawak, Malaysia.

Materials and Methods

A cross-sectional study was carried out in both urban and rural areas of Sibu town from January to March 2017. Sample size was calculated using Epi-info version 7.0 statistical package. The prevalence of PMS, confidence limits and confidence level were set at 20%[4], 5% and 95%, respectively. Altogether 255 women of reproductive age (i.e., between 18 and 45 completed years of age) were recruited into the study. Informed consent was taken and face-to-face interview was applied to get the necessary data. A pretested, structured questionnaire, developed in English language and back translated into Malay was used. Data entry and analysis was done using SPSS version 20 statistical package. Chi-squared test was utilized to assess the association between PMS and socio-demographic variables.

PMS was diagnosed based on the ACOG criteria.[9] Inclusion criteria used in the present study were (1) having regular menstrual cycle, (2) positive history of at least one affective symptom (anxiety, cravings, depression, angry outbursts, irritability, confusion, social withdrawal) and at least one somatic

symptom (breast tenderness, abdominal bloating, headache, swelling of extremities) with some limitation of daily activity and (3) the onset of symptoms must be during the week before menses in three cycles and relieved with the menstrual flow. The presence or absence of PMS was assessed for the past one year period from the date of data collection. Attitude towards PMS was assessed using three items of questionnaires with 5-point-Likert scale. Attitudinal status was categorized into two groups; positive (if total score was 11-15) and negative (if scores was < 11).

Results

A total of 255 women participated in the study. Socio-demographic characteristics and residence of the respondents are shown in Table 1.

Table 1: Socio-demographic characteristics and residence of study participants

Variables	Frequency (n=255)	Percent (%)
Age-group		
18 – 24	124	48.6
25 – 34	95	37.3
35 – 45	36	14.1
Ethnicity		
Malay	59	23.1
Chinese	61	23.9

Iban	98	38.5
Others	37	14.5
Employment status		
Employed	132	51.8
Un-employed	123	48.2
Education status		
Primary	22	8.6
Secondary	123	48.2
Tertiary	110	43.2
Residence		
Urban	155	60.8
Rural	100	39.2

The symptoms of PMS reported by the respondents are summarized in Table 2. Among the different presentations, the commonest is increase in appetite (63.1%), followed by acne (58.8%) and mood swings (56.1%). The least presentation experienced by the study participants is allergic reaction (3.1%).

Table 2: Symptoms of PMS

Symptoms	Frequency (n=255)	Percent
Appetite increase	161	63.1
Acne	150	58.8
Mood Swings	143	56.1
Food Cravings	134	52.5
Irritability	126	49.4
Oily Skin	126	49.4
Breast Tenderness	119	46.7
Fatigue	102	40.0
Headache	96	37.6
Backache	77	30.2
Lack of Concentration	71	27.8
Anxiety	69	27.1
Joint and Muscle Pain	57	22.4
Insomnia	55	21.6

Abdominal Bloating	54	21.2
Disinterest in daily activities	50	19.6
Weight gain	50	19.6
Nervous Tension	49	19.2
Crying	49	19.2
Hypersomnia	48	18.8
Forgetfulness	43	16.9
Frequent Urination	43	16.9
Sensitive to Rejection	42	16.5
Weakness Radiation Down Thighs	41	16.1
Diarrhoea	40	15.7
Feeling Overwhelmed	39	15.3
Depression	36	14.1

Interpersonal Conflicts	36	14.1
Confusion	33	12.9
Dizziness or Fainting	28	10.9
Palpitation	28	10.9
Fluid Retention	20	7.8
Constipation	19	7.5
Swollen Extremities	15	5.9
Hives	10	3.9
Allergic Reaction	8	3.1

The prevalence of PMS among study population was 44.3% (95% CI: 38.1%, 50.6%). Table 3 shows the prevalence of PMS by socio-demographic characteristics and residence. Age, ethnicity, education and residence were significantly related to the occurrence of PMS ($p < 0.05$).

Table 3: The occurrence of PMS by socio-demographic characteristics and residence

Variables	PMS	Total	

	Present (n=113)	Absent (n=142)	(n=255)	p-value
Age-group				
(completed years)	58 (46.8%)	66 (53.2%)	124 (100%)	
18 – 24	31 (32.6%)	64 (67.4%)	95 (100%)	0.002
25 – 34	24 (66.7%)	12 (33.3%)	36 (100%)	
35 – 45				
Ethnicity				0.026
Malay	23 (39.0%)	36 (61.0%)	59 (100%)	
Chinese	21 (34.4%)	40 (65.6%)	61 (100%)	
Iban	55 (56.1%)	43 (43.9%)	98 (100%)	
Others	14 (37.8%)	23 (62.2%)	37 (100%)	
Employment				0.527
status	61 (46.2%)	71 (53.8%)	132 (100%)	
Employed	52 (42.3%)	71 (57.7%)	123 (100%)	
Un-employed				
Education status				0.033
Primary	13 (59.1%)	9 (40.9%)	22	
Secondary	61 (49.6%)	62 (50.4%)	123	
Tertiary	39 (35.5%)	71 (64.5%)	110	
Residence				<
Urban	60 (60.0%)	40 (40.0%)	100 (100%)	0.001
Rural	53 (34.2%)		155 (100%)	

		102 (65.8%)		

More than half of the respondents (56.1%; 95% CI: 49.8%, 62.3%) had positive attitude towards PMS. Although age, ethnicity, residence and education status were found to have significant association with having positive history of PMS, none of them were significantly related to the attitude towards PMS (Table 4).

Table 4: The attitude towards PMS by socio-demographic characteristics and residence

Variables	Attitude towards PMS		Total (n=255)	p-value
	Positive (n=143)	Negative (n=112)		
Age-group				
18 – 24	65 (52.4%)	59 (47.6%)	124 (100%)	0.442
25 – 34	58 (61.1%)	37 (38.9%)	95 (100%)	
35 – 45	20 (55.6%)	16 (44.4%)	36 (100%)	
Ethinicity				
Malay	37 (62.7%)	22 (37.3%)	59 (100%)	
Chinese	34 (55.7%)	27 (44.3%)	61 (100%)	0.523
Iban	50 (51.0%)	48 (49.0%)	98 (100%)	

Others	22 (59.5%)	15 (40.5%)	37 (100%)	
Employment status				0.310
Employed	70 (53.0%)	62 (47.0%)	132 (100%)	
Un-employed	73 (59.3%)	50 (40.7%)	123 (100%)	
Education status				0.952
Primary	13 (59.1%)	9 (40.9%)	22	
Secondary	69 (56.1%)	54 (43.9%)	123	
Tertiary	61 (55.5%)	49 (44.5%)	110	
Residence				0.203
Urban	61 (61.0%)	39 (39.0%)	100 (100%)	
Rural	82 (52.9%)	73 (47.1%)	155 (100%)	

Discussion

The most prevalent symptoms experienced by the respondents were increased appetite, acne, mood swings, food cravings, irritability, oily skin, breast tenderness and fatigue. More or less the same symptoms were reported by similar studies done in different countries such as India[10,11], Pakistan[12], China[4], and Iran.[13]

This study provides information on the prevalence of PMS among women of reproductive age in Sibu and their attitude towards PMS. The prevalence of

PMS among study population was 44.3%. This is much higher than those of studies conducted among students from secondary school in Sri Lanka (8.8%)[14] and among college students in India (18.4%).[15] However, the prevalence of PMS determined by the present study is lower than those reported in studies done among secondary school students in Seremban, Malaysia (74.6%)[3], and among university students in Egypt (56.1%)[16] and Iran (98.2%).[13] Besides, the prevalence of PMS revealed in similar community based studies carried out in France[5], Spain[8] and China[4] were 12.2%, 8.9% and 21.1%, respectively while institution based studies conducted in Saudi Arabia[17] and Inida[11] reported that the prevalence of PMS among women of reproductive age were 56% and 67%, respectively. The differences of age, socio-cultural characteristics such as education, occupation etc. and awareness on PMS among study populations could explain these findings. The utilization of different diagnostic criteria should also be taken into consideration in comparing the prevalence of PMS among various studies. Direkvand-Moghadam and colleagues[18] concluded in their study that the use of various measurement tools and the difference in study population were solely responsible for the differences in the reported prevalence of PMS among studies. However, the pooled prevalence of PMS worldwide (47.8%) and in Asia (46%) reported in a meta-analysis[18] were almost similar to that of present study (44.3%).

In this study, age, education status, ethnicity and residence of the respondents were significantly related to the occurrence of PMS. Previous studies also

revealed similar findings. Independent studies conducted in India and Pakistan reported that residence[19], education[19,20] and age[21,22] were significantly associated with the prevalence of PMS.

In this study, more than half of the respondents (56.1%) had positive attitude towards PMS. This finding is consistent with those found in similar studies carried out in Kelantan, Malaysia[23], Spain[8] and UK.[24] This might be due to the fact that women in Sibu may be knowledgeable or have a generally high tolerance towards the symptoms of PMS. However, no clear associations could be elicited between socio-demographic factors and attitudes.

Conclusion

A significant proportion of women of reproductive age in Sibu, Sarawak, Malaysia had positive history of PMS and they should be encouraged to seek out appropriate treatment. Age, ethnicity, residence and education status were significantly associated with the occurrence of PMS but not with attitude.

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Original article

Design of Transdermal Delivery Patches of Diclofenac Sodium Using Different Concentrations of Hydroxypropyl Methylcellulose and Evaluation on the Physicochemical and Dissolution Profile of the Patches

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Abstract

Background: Long term use of oral diclofenac sodium is associated with higher risk of adverse effects. Diclofenac sodium which is formulated in transdermal drug delivery system (TDDS) shows a lower rate of non-steroidal anti-inflammatory drugs (NSAIDs) associated adverse effects and at the same time providing sufficient pain relief. **Aim:** The aim of this study was to determine the effect of different concentrations of hydroxypropyl methylcellulose (HPMC) on the physicochemical properties and dissolution profile of diclofenac sodium transdermal patches. **Materials and Methods**: Different formulation of diclofenac sodium transdermal patches had been formulated using the solvent evaporation method. Each of the formulation was evaluated based on the parameters of moisture content, flatness, thickness and folding endurance. A paddle type of dissolution tester was used to investigate the in vitro drug release profile of formulation F1, F3, and F5 of the diclofenac sodium transdermal patches. One-way ANOVA test with post hoc analysis was used to analyse the moisture content, thickness, folding endurance, and dissolution tests. **Results:** The results of the physicochemical tests showed that increase in concentrations of HPMC would increase the moisture content and thickness of the diclofenac sodium transdermal patch. On the other hand, other physicochemical properties such as flatness and folding endurance of the diclofenac sodium transdermal patch were not affected by change in the concentrations of HPMC. Formulations F1, F3 and F5 showed optimum results because these formulations possesses suitable physicochemical characteristics, including moisture content, flatness and folding endurance. The in vitro drug release study revealed that increase in the concentrations of HPMC would increase the time taken for the drug to diffuse out from the polymer matrix of transdermal patch. **Conclusion:** This study showed that change in the concentrations of HPMC would affect the physicochemical properties such

Keywords: Transdermal, Patch, Diclofenac, Hydroxypropyl Methylcellulose, HPMC

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Introduction

Pain is an unpleasant feeling that causes negative effects in several areas of a person's life, including emotion, thought, normal daily activities and comfort[1]. Nowadays, there is an increase in the popularity of painkiller, such as non-steroidal anti-inflammatory drugs (NSAIDs) secondary to the increasing prevalence of work-related musculoskeletal pain[2]. Oral formulation of NSAIDs such as diclofenac sodium tablet has been regularly prescribed and dispensed to treat mild to moderate musculoskeletal pain and it is proved to be effective in managing such disorder. However, long term use of oral diclofenac sodium is associated with higher risk of adverse effects such as cardiovascular disease, gastrointestinal ulceration and renal dysfunction[3–5]. Hence, topical formulation of diclofenac sodium has been introduced to minimise the adverse effects of the oral diclofenac sodium by maximising the local exposure and decreasing the systemic exposure of diclofenac sodium[6].

Hydroxypropyl methylcellulose (HPMC) is a novel hydrophilic and swellable polymer that is commonly used in TDDS to regulate the drug release kinetics. HPMC is a film forming polymer that possesses few properties such as it acts as a surface active agent, which is capable of adsorbing water and provide lubricity, easy dispersion and soothing feel during its application on the skin. HPMC rarely shows any significant interaction with other excipients or drugs when they are mixed together in the formulation. Moreover, HPMC is also able to produce a uniform film which is light and non greasy[7].

Few studies had been carried out by other researchers to study the formulation of diclofenac transdermal patches. Out of these studies, different types of polymers, including HPMC, had been incorporated together with the diclofenac transdermal patch and all of the polymers showed good compatibility with the drug[8–10]. However, the range of concentrations of HPMC which had been studied by them were narrow, which typically ranged from 1% w/v to 3% w/v. This may restrict one to determine the most suitable concentration of HPMC for the formulation of diclofenac transdermal patch. Hence this research was focused on investigating the effect of different concentrations of HPMC (ranged from 1% to 6% w/v) on the physicochemical properties and dissolution profile of diclofenac transdermal patches.

MATERIALS AND METHOD

Materials and equipment's

List of chemicals

Hydroxypropyl methylcellulose, M.N. 86,000; viscosity 4,000 cP (2% solution), ACROS Organics™, Diclofenac sodium, 98%, ACROS Organics™, and Methanol, Certified AR for analysis that were purchased from Fisher Scientific (Malaysia). 12-Propylene Glycol C.P that was purchased from R&M Chemicals (Malaysia).

List of equipment's

DU ®730 UV-Vis Spectrophotometer (Beckman Coulter), TDT-080L Dissolution Tester (Electrolab), AL204 Analytical Balance (Mettler Toledo), Spectrum 100 FTIR Spectrophotometer (Perkin Elmer), Lambda 25 UV/VIS Spectrophotometer (Perkin Elmer), and Fisherbrand™ Isotemp™ Basic Stirring Hotplate: Model 11-102-505H (Fisher Scientific).

Preparation of transdermal patches

The diclofenac sodium transdermal patch was prepared using solvent casting method that was adapted from the study by Singh and Bali[11]. In brief, specific amount of HPMC powder, propylene glycol and diclofenac sodium powder were dissolved in methanol and mixed homogeneously with magnetic stirrer. 10 mL of the mixture was withdrawn with graduated pipette and transferred into a silicone mould with 7.8 cm length and 5.3 cm width. The silicone mould was placed horizontally on a flat surface and the solution was allowed to dry at the room temperature of 27 $\pm$ 1.5 °C and relative humidity of 65 $\pm$ 2%

for 24 hours. After 24 hours, the transdermal patch was taken out from the mould and cut into smaller size of patches, with length of 4 cm and width of 2 cm. These transdermal patches were wrapped with aluminium foil and stored properly before proceeding to evaluation studies. The above steps were repeated to fabricate the formulations F2, F3, F4, F5, and F6 where each of the formulation contained different concentration of HPMC. The amount of materials used in each formulation was shown in the Table 1.

Table 1: **Formulation of diclofenac sodium transdermal patch**

Formulation	HPMC (% w/v)	Propylene glycol (% w/w)	Diclofenac sodium (mg)	Methanol (mL)
F1	1	30	250	50
F2	2	30	250	50
F3	3	30	250	50
F4	4	30	250	50
F5	5	30	250	50
F6	6	30	250	50

Evaluation of transdermal patch

Physical appearance

All the formulated patches were visually inspected for smoothness, clarity, and colour.

Percentage moisture content

The evaluation study on the moisture content of transdermal patch was based on the method reported by Ubaidulla et al, .[12] The initial weight of a transdermal patch was weighed using an analytical balance and the result was recorded as m_1. Then, the transdermal patch was placed into a desiccator containing active silica gel beads for 24 hours. After 24 hours, the weight of the transdermal patch was measured again using the same analytical balance and the result was recorded as m_2. The moisture content of a transdermal patch was calculated using the formula:

$$\%\ Moisture\ Content = \frac{m_1 - m_2}{m_1} x\ 100\%$$

Where m_1= Initial weight of the patch (g)

m_2= Final weight of the patch (g)

Flatness

The initial length of a transdermal patch was measured and the reading was recorded as l_1. After this, the patch was cut longitudinally into three strips; where one strip from the centre and the remaining two from the side of the patch. The length of the cut strips were measured again and the reading were recorded as l_2 [13]. The following formula was used to calculate the flatness of a diclofenac sodium transdermal patch:

$$\% Constriction = \frac{l_1 - l_2}{l_1} x\ 100\%$$

$$\% Flatness = 100\% - \% Constriction$$

Where l_1= Initial length of the strips (cm)

l_2= Final length of the strips (cm)

Thickness

The thickness of a transdermal patch was measured at three different locations with a micrometer screw gauge, and the mean thickness was calculated for each of the patch[14].

Folding endurance

The folding endurance of a patch was determined by continuously folding at the centre of the patch until it was broken or a crack was shown. The total folding count right before the patch was broke or showed any crack was indicated as folding endurance value[12].

Compatibility study

The compatibility of diclofenac sodium with other excipients was determined through the Fourier Transform Infrared (FTIR) spectroscopic study. Samples of pure diclofenac sodium powder, propylene glycol, HPMC powder, methanol and the mixture of diclofenac sodium, propylene glycol, HPMC and

methanol were prepared and analysed through FTIR spectrophotometer. The infrared spectrum of each of the samples were recorded and compared with each other.

***In vitro* drug release**

Phosphate buffer of pH 7.4 was used as dissolution medium during the dissolution process. Paddle type of dissolution tester was used with each dissolution vessel was filled up with 500 mL of phosphate buffer. The dissolution tester was set at temperature of 32 ± 0.5 °C and rotation speed of 50 rpm[15]. A stainless steel woven wire mesh was used as a sinker to hold the transdermal patch and prevented it from floating during the dissolution process.

The transdermal patch was assembled between the wire mesh and placed at the bottom of the vessels and centred using a glass rod. During the dissolution process, 5 mL of sample was withdrawn at the interval of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 40, 50, 60, 75, 90, 105, 120, 150, and 180 minutes. The drug contents in the withdrawn samples were analysed using ultraviolet-visible (UV-visible) spectrophotometer at maximum wavelength of 277 nm (Figure 1). The *in vitro* drug release study had been done on the formulation F1, F3, and F5. However, formulations F2, F3 and F6 were omitted from drug release assay due to large standard deviation in the physicochemical characteristics, including moisture content, folding endurance and thickness.

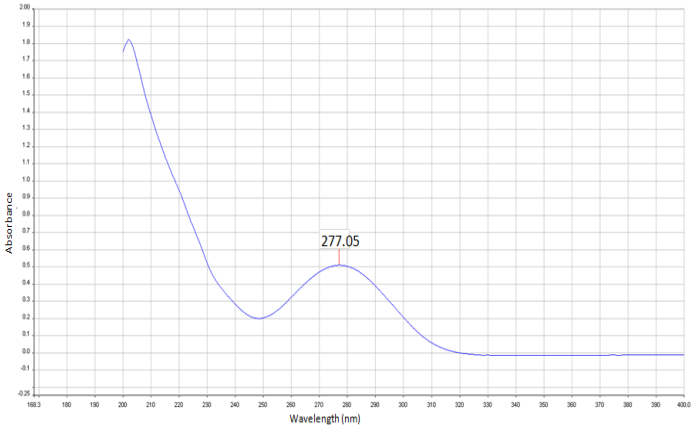


Figure 1: The diclofenac sodium shows the maximum absorbance at wavelength of 277 nm

Statistical analysis

IBM SPSS Statistics version 22 was used to carry out statistical analysis for the evaluation tests in this study. One-way ANOVA test with post hoc analysis was used to analyse the moisture content, thickness, folding endurance, and *in vitro* drug release tests.

RESULTS

Physicochemical properties

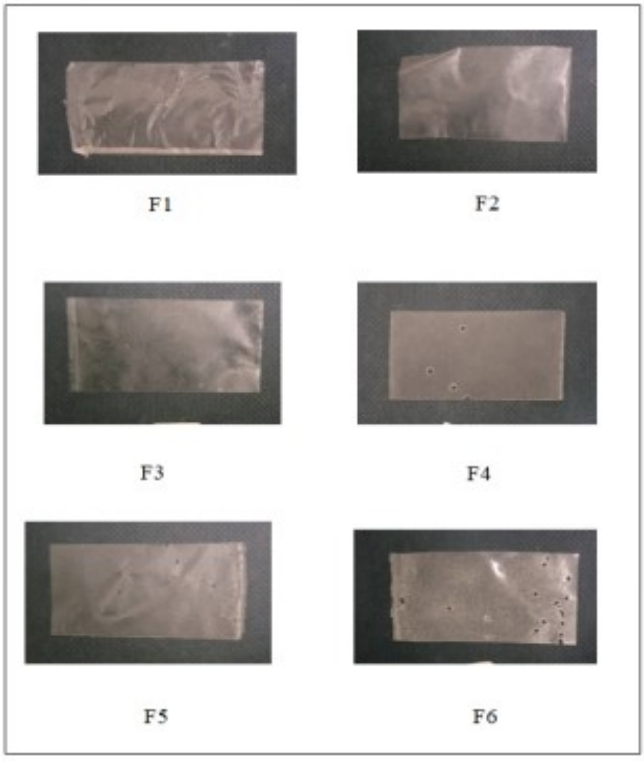


Figure 2: Formulation of diclofenac sodium transdermal patches

Table 2: Physicochemical properties of diclofenac sodium transdermal patches with different concentration of HPMC *Sample size = 3

Formulation	F1	F2	F3	F4	F5	F6
Colour	Colourless	Colourless	Colourless	Colourless	Colourless	Colourless
Clarity	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
Smoothness	Smooth	Smooth	Smooth	Smooth	Smooth	Not smooth
Moisture Content (%)*	2.000 ± 0.630	2.685 ± 0.840	3.505 ± 1.432	3.766 ± 2.196	3.954 ± 0.466	4.577 ± 0.784
Flatness (%)*	100	100	100	100	100	100
Folding Endurance*	150.333 ± 5.508	259.333 ± 29.006	168.667 ± 58.526	370.000 ± 152.355	151.333 ± 37.647	72.000 ± 15.716
Thickness (cm)*	0.0633 ± 0.0173	0.0656 ± 0.0201	0.1167 ± 0.0224	0.1511 ± 0.0196	0.1622 ± 0.0211	0.2311 ± 0.0220

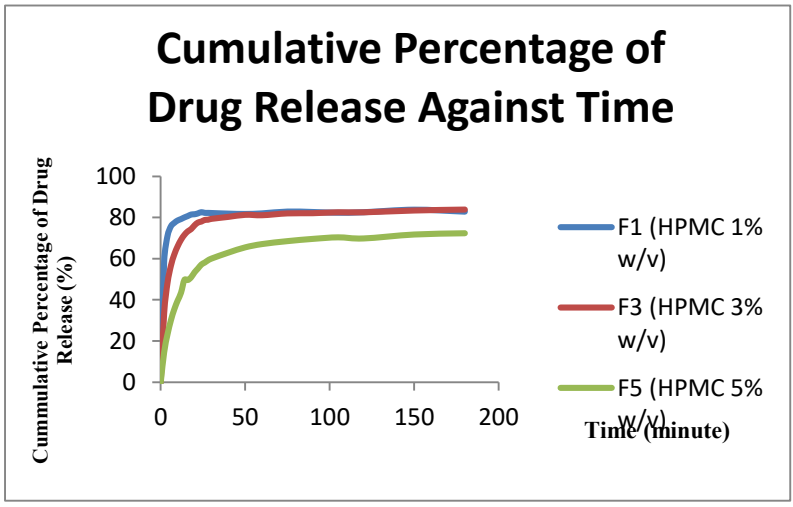
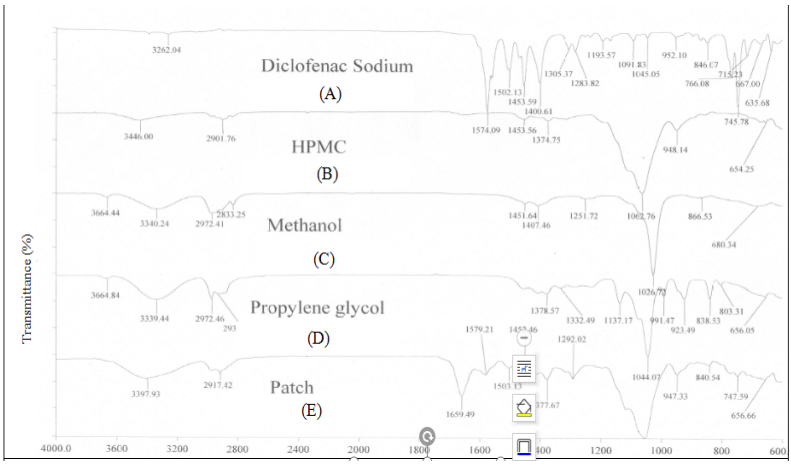


Figure 3: *In vitro* drug release profile of formulation F1, F3, and F5 diclofenac sodium transdermal patch (Graph of cumulative percentage of drug release against time). Sample size= 12

Compatibility study



Wavenumber (cm^{-1})

Figure 4: FTIR spectrum of (A) diclofenac sodium, (B) HPMC, (C) methanol, (D) propylene glycol, (E) mixture of diclofenac sodium and excipient

DISCUSSION

Physical appearance

All the formulations with different concentrations of HPMC were able to form colourless and transparent patches. All patches had smooth appearance except

formulation F6. This might due to solution used in formulation F6 during the solvent casting process was too viscous and led to uneven spread of the solution on the mould. This resulted in non smooth appearance in F6 patches.

Moisture content: The lowest moisture content was observed in formulation F1 and the highest moisture content was observed in formulation F6. Generally, the moisture content of diclofenac sodium transdermal patches increased with the increased of HPMC concentrations. This might be due to the presence of hydroxyl and ether functional group in HPMC, which favoured the hydrogen bonding of water molecules in the environment[16]. There were more sites available for hydrogen bonding within the HPMC molecules with increasing concentrations of the HPMC. Hence, higher the concentration of HPMC, the more water molecules from the environment would be attracted to form hydrogen bond with the polymer, which resulted in higher amount of moisture content in the formulation. Nevertheless, the result of one-way ANOVA test showed that the change in the moisture content due to different amount of HPMC was not significant (p-value > 0.05).

Currently, there was no maximum limit requirement for the moisture content in a transdermal patch. Based on the studies conducted by Ramadan et al.[16], Garala et al.[17], Garud et al.[18], Kumar et al.[19], Thakur et al.[20] , a transdermal patch with moisture content value of less than 5% was considered as low and acceptable. Low moisture content could prevent the patches from breakage or cracking due to the presence of water as natural plasticiser[21]. In addition, the

low moisture content in the transdermal patches increases the stability of the patches and prevents microbial contamination in the formulations[14]. The percentage moisture content of the patches which were fabricated in this research were ranged from 2.000 to 4.577%. Thus the moisture content for all the formulations were considered as low and acceptable.

Flatness: The results of the evaluation test showed that all formulations had 100% flatness. This indicated that all the patches did not exhibit any sign of constriction. Hence, all the patches from the formulations with the concentrations of HPMC ranged from 1% w/v to 6% w/v had smooth and flat surfaces[8]. Moreover, the results also implied that the change in the concentration of HPMC in the formulation would not have any effect on the flatness of the transdermal patches. This experiment was conducted at laboratory with controlled temperature, light and humidity. Factors such as heat, light and humidity have less impact on the stability of the HPMC.

Thickness: Physical evaluation test showed that the thickness of diclofenac sodium transdermal patches would increase with the increase in concentration of HPMC. This phenomenon was also found to be similar with the process of making thin film coating of the tablet, where the increased polymer concentration would increase the thickness of the thin film.[22] From one-way ANOVA test, it is showed that there was a significant difference (p-value < 0.05) between the thickness of transdermal patches of varying concentrations. In the post hoc analysis, the results were significant (p-value < 0.05) for all

formulations except the comparison between the thickness of formulation F1 with F2, and F4 with F5.

The thickness of transdermal patch is important as it determines the rate of drug release from the matrix form of transdermal patch.[23] Referring to the "Guideline of Quality of Transdermal Patch" published by European Medicines Agency, there was no reference value for the thickness of the formulated transdermal patch. The thickness of the patch would be accepted as long as it is justified rationally[24].

The experiment result, showed that the formulated transdermal patches for six formulations had large relative standard deviations (RSDs) (range from 8.994% to 28.863%). The large RSDs for all the formulations indicated that the thickness of the patches were not uniform. This might be due to the unequal distribution of HPMC during the solvent casting process. Furthermore, transdermal patches with non-uniform thickness might affect the overall rate of drug release from the formulation. A study conducted by Imani et al, .[25] showed that the rate of drug release from a TDDS was affected by the thickness of the patch. This phenomenon might be explained by the Fick's law of diffusion:

$$J = \frac{DP}{h} \times C \times A$$

Where D = Diffusion coefficient

J = Flux

P = Partition coefficient of drug

h = Thickness

C = Concentration

A = Surface area

Based on the Fick's law of diffusion, the diffusion of the drug from the polymer would be affected by the thickness of the polymer matrix. A highly varied thickness of a transdermal patch would result in varied drug release in the transdermal patch[26, 27]. Hence all the formulations in this study did not have a satisfactory thickness value. A larger sample size should be included to decrease the standard deviation of this evaluation test.

Folding endurance: A study by Bala and Sharma[28] reported that the folding endurance of a polymeric film increased with the concentrations of polymer. Moreover, B. Vyas et al.[29] proposed that there was a strong correlation between the concentration of HPMC and the folding endurance of the polymeric film.

From the result of one-way ANOVA test of this experiment, change in the concentrations of HPMC in the formulations had a significant effect on the folding endurance (p-value < 0.05). However, the findings in this experiment are not consistent with reported results conducted by other researchers. It was observed that the folding endurance values were not increased according to

the concentration of HPMC added into the formulation. The fluctuation of value might be due to random error, where the force applied to fold a transdermal patch each time was not consistent. This resulted in non-equal force being applied on the folded area and caused the fluctuation on the folding endurance value. Thus, a higher sample size should be included in this evaluation test to minimize such error.

The aim of the folding endurance test was to evaluate ability of the patch to endure with such folding force[30]. When the transdermal patch was applied on the skin, the patch might have been folded when there were body movements. Even though it is one of the important parameters in the evaluation of transdermal patch, there are no guidelines or pharmacopoeia indicated for folding endurance of a transdermal patch, but based on other studies that had been conducted by other researchers, an ideal transdermal patch should have folding endurance of not less than 100[14,31,32]. Referring to the results of this study, all the formulations except formulation F6 exhibited acceptable folding endurance.

Compatibility study: Figure 4 (E) showed the mixture of diclofenac sodium were still preserved, such as –C=O stretch (1659.49 cm^{-1}) and –C–Cl stretch (747.59 cm^{-1}). The peaks at wavenumbers of 3397.93 cm^{-1} and 2917.42 cm^{-1} represented as –O-H stretch and –C-H stretch respectively. The presence of these peaks could be due to the presence of excipients such as HPMC or propylene glycol[33]. Thus, it could be concluded that no new peak was observed

in Figure 4 (E). These indicated that there was no major interaction between the diclofenac sodium with the other excipients[34].

There was a slight change in the FTIR spectrum of mixture of diclofenac sodium and excipients. This could likely be due to formation of hydrogen bond between the drug and excipients. Nonetheless, the *in vitro* drug release profile from the dissolution studies showed that these interaction did not interfere with the release of diclofenac sodium from the HPMC polymer matrix[35].

In vitro drug release study: Formulations F1, F3 and F5 were selected for the *in vitro* drug release study because the formulations possessed acceptable physicochemical characteristics, including moisture content, flatness and folding endurance.

Figure 3 showed that all the formulations had initial burst release of drug from 0 to 10 minutes, followed by a constant drug release from 12 to 180 minutes. Similar results were reported by Vora et al.[36], where HPMC was also used as the polymer in the formulation of transdermal patch in their study. The experiment showed that the initial burst release of drug could be attributed to the hydrophilic properties of the HPMC.

The dissolution study showed that there was significant difference in the percentage cumulative drug release between the formulations with varying concentrations of HPMC. This could refer to the one-way ANOVA test on the cumulative percentage of drug release at different time points. The difference

between the total amount of drug release of diclofenac sodium transdermal patch with varying concentrations of HPMC at each time interval from 2 minutes to 180 minutes were significant (p-value < 0.05).

In the post hoc analysis of one-way ANOVA, from the time interval of 2 to 10 minutes, it showed that the cumulative percentage drug release of F1 was significantly higher than F3 and F5 (p-value < 0.05). When the dissolution process proceeded to the time interval of 12 to 120 minutes, the difference in cumulative percentage drug release between formulations F1 and F3 was not significant (p-value > 0.05) as the drug release rate from both formulations started to reach plateau. Nevertheless, the cumulative percentage drug release of F5 was still significantly lower than F1 and F3 from time interval of 12 to 120 minutes (p-value < 0.05), and the drug release from the formulation F5 did not reach the plateau. At 150 minutes, there was no significant difference in the cumulative percentage drug release between the formulations (p-value > 0.05). Generally, it could be observed that formulation F1 reached the constant drug release first, followed by the F3 and F5. Thus, this indicated that, the higher the concentration of HPMC, the longer the time taken for the cumulative percentage drug release to reach plateau.

The phenomenon in this *in vitro* drug release study could be explained by the properties of HPMC. When the HPMC polymers were hydrated with water, the polymer would start to swell and changed from glassy matrix into gel-like structure. The mechanism of drug release from the HPMC matrix could be

either through drug diffusion or erosion of polymer matrix. However, diclofenac sodium was a water soluble drug, hence it was suggested that diclofenac sodium was released from the HPMC matrix mainly through diffusion method[37,38]. When the concentrations of HPMC increased, there would be increase in the physical cross-linking of the polymer chain, which in turn resulted in the higher chain entanglement in the HPMC matrix. This caused the diffusional pathway to become convoluted and the effective diffusion coefficient of the diclofenac sodium from the polymeric film would be reduced during the dissolution process[39]. Thus, higher the concentration of HPMC, higher the physical cross-linking of the polymer chain, slower diclofenac sodium to be diffused out from the polymer matrix.

CONCLUSION

This *in vitro* drug release study showed that changed in the concentration of HPMC had a significant effect on the percentage cumulative drug release of diclofenac sodium transdermal patch (p-value < 0.05). The higher the concentrations of HPMC, the longer it took for the drug to be released from the diclofenac sodium transdermal patches. This could be attributed to the varying amount of physical cross-linking of the HPMC polymer when different concentrations of HPMC were used in the formulation.

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Original article

Formulation and Evaluation of Transdermal Drug Delivery Film of Diclofenac Sodium Using Polyvinylpyrrolidone as Film-Forming Agent

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Abstract

Background: Diclofenac sodium has been widely used to reduce inflammation, fever and pain in patients. Oral administration of diclofenac sodium was associated with adverse effects of gastric ulcer and gastrointestinal bleeding. Transdermal drug delivery film has been practiced to replace oral dosage form to minimize side effects. ***Aim***: The aim of this study was to study the drug-polymer interaction between diclofenac sodium and polyvinylpyrrolidone (PVP).

Materials & method : Concentrations of PVP ranging from 3% w/v to 8% w/v, propylene glycol, citric acid anhydrous and methanol were used to formulate transdermal drug delivery film and diclofenac sodium was used as active pharmaceutical ingredient. Solvent evaporation technique was used to formulate transdermal films. All the six formulations were subjected to drug-polymer interaction study and evaluation of physico-chemical characteristics including thickness, weight variation, moisture content, folding endurance and *in vitro* drug release.

Results: Formulated transdermal films showed increased thickness of films with increase in PVP concentrations. However, inconsistent results of weight variation, moisture content and folding endurance were observed when the concentration of PVP increased. *In vitro* drug release study showed that when PVP concentration increased, the drug release also increased. At the beginning of dissolution, a rapid release for more than 50% of the drug was observed. Based on the drug release profile, transdermal films formulated with 8% w/v PVP concentration were preferred in this study as it had the highest drug release among the three formulations that were selected to conduct drug release study.

Conclusion: Diclofenac sodium and PVP can be incorporated and concentrations of PVP has an influence on the physico-chemical characteristics and *in vitro* drug release.

Keywords: Diclofenac Sodium, Polyvinylpyrrolidone, Solvent Evaporation Technique, Rapid Drug Release, Burst Release

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Introduction

Transdermal drug delivery system (TDDS) is defined as topically administered medications in self-contained, discrete dosage forms of patches that deliver drugs through the skin portal to systemic circulation at a predetermined controlled rate over a prolonged period.[1] TDDS has become important over the years in pharmaceutical sciences, as it has prominent advantages over limitations of oral route and injectable route as it bypass the first pass metabolism and avoid painful administration. [2] Besides, it increases patient compliance by reducing dosing frequency and provides prolonged action of drug therapy. [3,4]

Diclofenac sodium is a non-selective non-steroidal anti-inflammatory drug (NSAID). This drug is under the class of phenylacetic acid where it is commonly used as analgesic, anti-inflammatory and antipyretic effect.[5] Diclofenac sodium undergoes first pass metabolism and it has low oral bioavailability. Due to the first pass metabolism, it causes gastrointestinal side effects including gastric ulceration and gastrointestinal bleeding.[6] On physical

appearance diclofenac sodium are white or slightly yellowish, hydrophilic in nature, slightly hygroscopic and crystalline in powder.[7]

Polyvinylpyrrolidone (PVP) also known as povidone, is a synthetic polymer that is hydrophilic in nature and it is soluble in aqueous and alcoholic solution. [8] PVP acts as film-forming agent in TDDS to control the drug release from the polymer matrix.[9] Moreover, the use of PVP in formulating TDDS can inhibit formation of recrystallisation and hence improves physical stability of the pharmaceutical disperse system.[10]In this research an attempt was made to study the drug-polymer interaction of diclofenac sodium with PVP.

Materials and methods

Materials

Diclofenac sodium with 98% purity was purchased from Fisher Scientific (M) Sdn. Bhd. Polyvinylpyrrolidone (PVP), methanol, polyethylene glycol 400 (PEG 400), propylene glycol and citric acid anhydrous were purchased from Synertec Enterprise Sdn. Bhd, Malaysia. PVP and methanol were analytical reagent grade, whereas propylene glycol and citric acid anhydrous were chemically pure grade.

Apparatus

AL204 analytical balance manufactured by Mettler Toledo, Spectrum 100 FTIR spectrophotometer manufactured by Perkin Elmer, TDT-080L Dissolution Tester manufactured by Electrolab and DU® 730 Ultraviolet-

Visible Spectrophotometer manufactured by Beckman Coulter were the apparatus used in this research study.

Methods

Preparation of stock solution containing diclofenac sodium

A stock solution of diclofenac sodium with concentration of 1.5 mg/mL was prepared whereby methanol was used as the suitable solvent because diclofenac sodium and PVP were readily soluble in alcohol. [11]

Preparation of transdermal films

Transdermal films containing diclofenac sodium were formulated by solvent evaporation technique.[12] The suitable amount of plasticisers used to formulate transdermal films was 20% w/w of the amount of PVP used.[13] Therefore, 10% w/w of propylene glycol and 10% w/w citric acid anhydrous were incorporated as plasticisers. Six different compositions of transdermal films with different concentrations of PVP and the amount of plasticisers were labelled with a corresponding formulation code (Table 1).

After all the excipients were completely mixed, the solution was left static to ensure air bubbles were released out from the solution. Then, 10 mL of the solution was withdrawn and casted on silicone mould with the approximate area of 44 cm^2. Subsequently, the polymeric solution in the silicone mould was allowed to dry at room temperature (approximately 27˚C, 65% humidity) for 24 hours. [12] After 24 hours of drying, the large films (44 cm^2) were removed

from the silicone mould. Lastly, each large film was cut into 3 cm x 3 cm (9 cm^2). Most importantly, every evaluation of the transdermal films were done on freshly prepared transdermal films. PVP in different concentrations of 3% w/v, 4% w/v, 5% w/v, 6% w/v, 7% w/v and 8% w/v were represented as formulation codes of F1, F2, F3, F4, F5 and F6 respectively (Table 1).

As the propylene glycol used in this research study was in liquid form, the amount of propylene glycol required in milliliters was calculated by using the equation of density as showed below:

$$\text{Density} = \frac{\text{Mass (g)}}{\text{Volume (mL)}}$$

Where,

Density of propylene glycol was 1.04 g/mL;
Mass represents as the amount of propylene glycol required in gram;
Volume represents as the amount of propylene glycol required in milliliter.

Formulation code	**Concentration of PVP (% w/v)**	**Amount of PVP (g)**	**Amount of plasticisers**		**Volume of stock solution containing diclofenac sodium (mL)**
			Propylene glycol (mL)	Citric acid anhydrous (g)	
F1	3	1.8	0.17	0.18	60

F2	4	2.4	0.23	0.24	60
F3	5	3.0	0.29	0.30	60
F4	6	3.6	0.35	0.36	60
F5	7	4.2	0.40	0.42	60
F6	8	4.8	0.46	0.48	60

Table 1: Six different compositions of transdermal films.

Evaluation of transdermal films

Drug-polymer interaction

Interaction between drug and polymer was evaluated by Fourier Transform Infrared (FTIR) spectrophotometer [12] where Spectrum 100 FTIR spectrophotometer manufactured by Perkin Elmer was used in this research study. First, the transdermal film of diclofenac sodium with PVP was formulated using solvent evaporation technique where methanol was used as the solvent. The transdermal films were formulated without incorporating any excipients. The formulated transdermal films and diclofenac sodium powder with 98% purity were scanned in the ranged from 4000 cm^{-1} to 800 cm^{-1} [14]. The characteristic peaks present in FTIR spectrum were interpreted.

Physical observations

Three freshly formulated films from each formulation were physically observed and examined based on homogeneity, colour, transparency and smoothness.[15] All the physical characteristics were recorded.

Thickness

Five different points were measured by using a micrometer screw gauge (Figure 1). [16,17] . The study was conducted in triplicate for each formulation on the transdermal films of 9 cm^2. The thickness was recorded and the mean and standard deviation were calculated. Each formulation, three formulated films (n=3) were used for the evaluation of thickness. Five different points were measured on each film and the mean thickness and standard deviation of five different points was calculated and recorded.

Figure 1: Indicator of points for thickness measurement.

Weight variation

The weight of formulated transdermal film was calculated as the weight difference between the weight of formulated transdermal film with a piece of aluminum foil and aluminum foil.[12] The study was conducted in triplicate for each formulation on the transdermal films of 9 cm^2. The mean and standard deviation of three formulated films were calculated and recorded.

Moisture content

The initial weight of formulated films was weighed individually by using AL204 analytical balance and the readings were recorded. Then, formulated films were kept for 24 hours in a desiccator containing silica gel bead. After 24 hours, the formulated films were weighed again using the similar AL204 analytical balance until a consistent weight was obtained. [18] A consistent weight was considered when the formulated films showed three similar consecutive readings of weight on the AL204 analytical balance. The mean and standard deviation of percentage moisture content of three formulated films (n=3) from each formulation were calculated and recorded. Percentage of moisture content was calculated based on the formula below:

$$\text{Percentage of moisture content} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Final Weight}} \times 100\%$$

Folding endurance

Three transdermal films with 9 cm^2 were subjected to folding endurance study by repeatedly folding the formulated films at the center until a noticeable break mark was observed. The number of times the formulated films folded at the center without a present of break marks was counted as the value of folding endurance. [17] The mean and standard deviation of three formulated films from each formulation were calculated.

In vitro drug release

The drug release of diclofenac sodium from the formulated films were assessed by modified paddle over disc method. The dissolution test for formulation F4, F5 and F6 were performed using TDT-080L Dissolution Tester manufactured by Electrolab with a stainless steel mesh as disc. The mesh was used to ensure the film maintained at the bottom of the vessel throughout the dissolution process.[19] 500 mL of phosphate buffer solution at pH 7.4 was prepared and the temperature was equilibrated to 32 ± 0.5˚C. Throughout the study, peddle rotated at 50 rpm. Throughout the process of dissolution, the vessels were covered with lids to minimise evaporation of the phosphate buffer solution. At the appropriate time interval, 5 mL of the aliquots was withdrawn through an inert filter and it was analysed at wavelength 277 nm by using DU® 730 Ultraviolet-Visible Spectrophotometer manufactured by Beckman Coulter. All the readings of absorbance were recorded. The concentration of diclofenac sodium was determined by

substituted the absorbance value into the equation (y= 0.043x – 0.0251, where, y indicate absorbance and x indicates concentration) obtained from the calibration graph of diclofenac sodium. Lastly, diclofenac sodium concentration was calculated and expressed as percentage of diclofenac sodium released.

The study was conducted in triplicate for formulation F4, F5 and F6 on 9cm^2 of formulated transdermal films. The result of diclofenac sodium released up to 180 minutes was recorded. Post hoc analysis was done on formulation F4, F5 and F6 at time points of 60, 120 and 180 minutes.

Results

Drug-polymer interaction

FTIR spectra of diclofenac sodium with 98% purity (Figure 2) and formulated transdermal film containing diclofenac sodium and PVP (Figure 3) were obtained by using FTIR spectrophotometer. The characteristic peaks of diclofenac sodium were 3262.04 cm^{-1}, 3402.50 cm^{-1}, 1574.09 cm^{-1} and 1654.89 cm^{-1}.

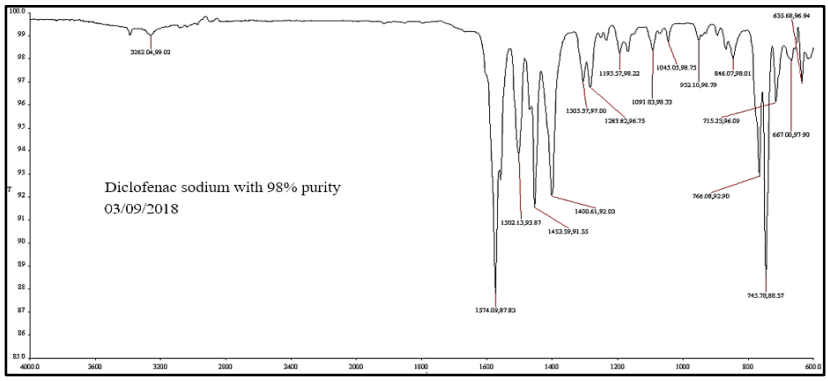


Figure 2: FTIR spectra of diclofenac sodium.

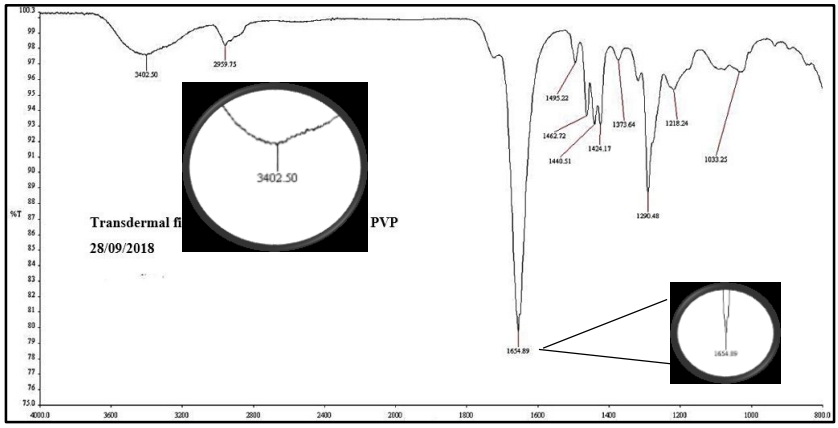


Figure 3: FTIR spectra of formulated transdermal film.

Physical Observations

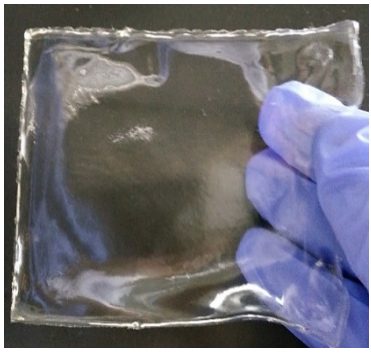
Based on Table 3 and Figure 4, physical appearances of three formulated films (9 cm^2) were observed for each formulation and all the formulated films were homogeneous, transparent, smooth and clear.

Formulation code	**Homogeneity*	**Colour*	**Smoothness*	**Transparency*
F1	Homogeneous	Transparent	Smooth	Clear
F2	Homogeneous	Transparent	Smooth	Clear
F3	Homogeneous	Transparent	Smooth	Clear
F4	Homogeneous	Transparent	Smooth	Clear
F5	Homogeneous	Transparent	Smooth	Clear
F6	Homogeneous	Transparent	Smooth	Clear

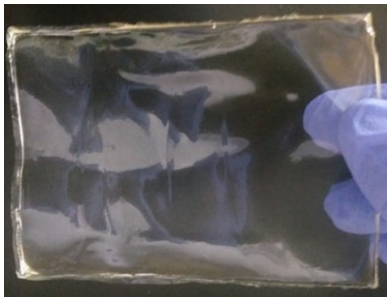
*Three formulated films (n=3)

Table 3: Physical appearance of formulated transdermal films.

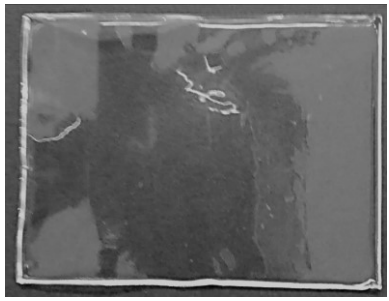
Formulation F1



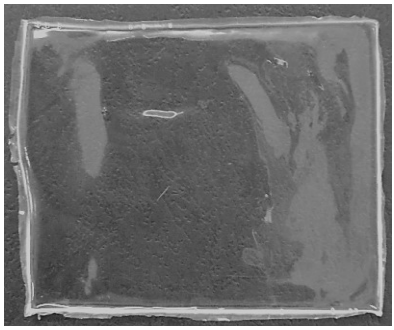
Formulation F2



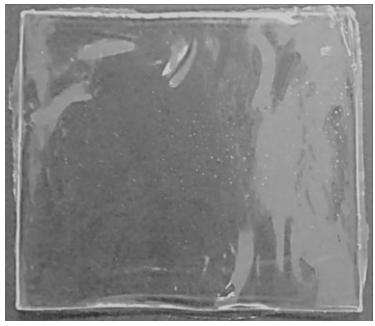
Formulation F3



Formulation F4



Formulation F5



Formulation F6

Figure 4: Physical observation of formulated transdermal films

Thickness

The mean thickness of the formulated films varied from 0.09 mm to 0.23 mm where F1 (0.09 ± 0.01) was the thinnest films and F6 (0.23 ± 0.02) was the thickest films among the six formulations. All the formulated films had a low

standard deviation, which was in between 0.01 and 0.02. This indicated that the thickness of formulated films was closed to the mean thickness according to the respective formulations.

Formulation code	*Mean (mm)	*Standard deviation
F1	0.09	0.01
F2	0.12	0.01
F3	0.13	0.02
F4	0.16	0.01
F5	0.18	0.01
F6	0.23	0.02

*Three formulated films (n=3)

Table 4: Thickness of formulated transdermal films.

Weight variation

Weight variation study was done three times (n=3) for each formulation and the weight of formulated films for six formulations were ranged from 0.0652 g to 0.1748 g that was recorded in Table 5. From the results, all formulated transdermal films did not significantly deviate from the average weight, as the value of standard deviation was low between 0.00 and 0.03. As the standard deviation was low, it indicated that the three formulated films from respective formulations were closed to the mean weight.

Formulation code	*Mean (g)	*Standard deviation
F1	0.0664	0.02
F2	0.0914	0.00
F3	0.0652	0.02
F4	0.1667	0.01
F5	0.1118	0.00
F6	0.1748	0.03

*Three formulated films (n=3)

Table 5: Weight variation of formulated transdermal films.

Moisture content

Based on Table 6 and Chart 1, the percentage of moisture content in the increasing order was F5, F3, F2, F4, F1 and F6. All the formulations had a high standard deviation ranged from 1.16 to 2.76, except for formulation F1 with a standard deviation of 0.58. Based on One-Way ANOVA analysis, the p-value was 0.631. This indicates that, the moisture content was not significantly difference with concentration of PVP as the p-value more than 0.05.

Formulation code	*Mean of percentage	*Standard deviation

	moisture content (%)	
F1	7.59	0.58
F2	6.62	1.57
F3	5.99	2.76
F4	7.10	1.16
F5	5.90	1.74
F6	8.68	2.04

*Three formulated films (n=3)

Table 6: Percentage of moisture content of formulated transdermal films.

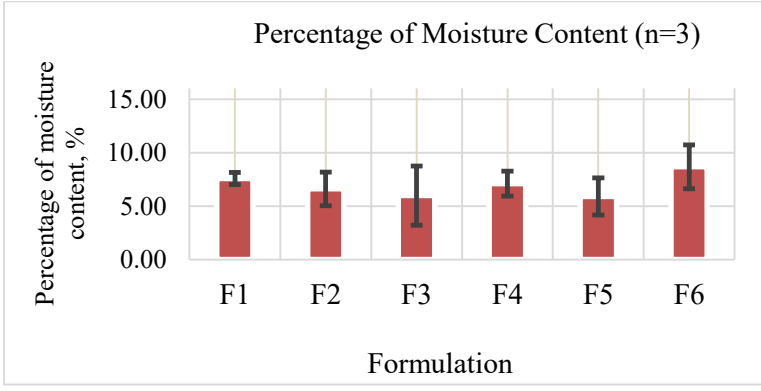


Chart 1: Percentage of moisture content of formulated transdermal films.

Folding endurance

Based on the results, the ascending order of folding endurance was F1, F2, F3, F6, F4 and F5. Among the six formulations, formulation F5 has the highest mean of folding endurance (162 folds) whereas formulation F1 has the lowest mean of folding endurance (1 fold). Although formulation F5 has excellent folding endurance, the standard deviation among the three formulated films was high that was 18.37. On the other hand, formulation F1 has the standard deviation of 0 with mean of folding endurance of 1 fold.

Formulation code	*Mean (folds)	*Standard deviation
F1	1	0.00
F2	2	0.47
F3	28	11.43
F4	59	8.22
F5	162	18.37
F6	52	7.12

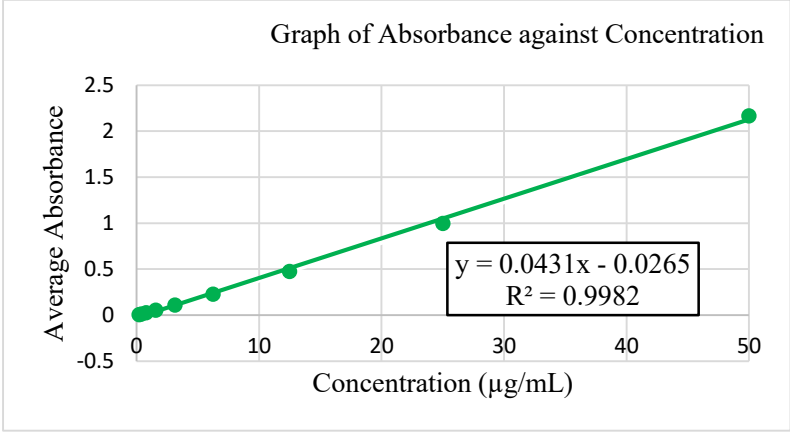
*Three formulated films (n=3)

Table 7: Folding endurance of formulated transdermal films.

Based on statistical analysis of One-Way ANOVA test, p-value was less than 0.05 at 95% confidence interval. This showed that there was a significant difference between the concentration of PVP with folding endurance.

***In vitro* drug release**

Regression equation was y = 0.0431x - 0.0265 and coefficient of determination was $R^2 = 0.9982$ (Graph 1). Moreover, the y-intercept from the regression equation was -0.0265 where the value of y-intercept was not significantly different from zero.



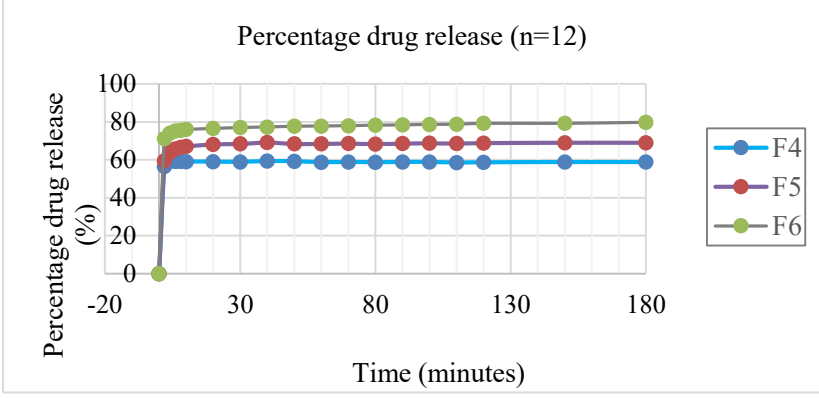
Graph 1: Calibration graph of diclofenac sodium.

The percentage of drug release from 60 minutes to 180 minutes showed an increasing trend for formulation F5 and F6 except formulation F4 showed fluctuate trend (Table 8). The phenomenon of fluctuating trend for formulation F4 was deceleration of drug release from 60 minutes to 120 minutes and then accelerated from 120 minutes to 180 minutes. A rapid released for more than 50% of the drug released was observed for first 2 minutes of dissolution (Graph 2).

Time (min) Formulation Code	*Percentage of drug release (%)		
	60	120	180
F4	58.78	58.67	58.80
F5	68.45	68.88	69.07
F6	77.84	79.27	79.79

*Twelve formulated films (n=12)

Table 8: Percentage drug release at 60, 120 and 180 minutes for three formulations.



Graph 2: Percentage drug release of three formulations up to 180 minutes.

Discussion

Drug-Polymer interaction

Drug-polymer interaction was studied by analysing the peaks from FTIR spectra. The-disappearance of characteristic peaks of the compound indicated that there was an interaction between drug and polymer.[20]

Characteristic peaks are summarized in (Table 2), characteristic peaks exhibited at 3262.04 cm^{-1} and 3402.50 cm^{-1} from Figure 2 and Figure 3 respectively indicated the presence of the amine functional group from the molecule of diclofenac sodium.[21,22] Moreover, characteristic peak at 1574.09 cm^{-1} and 1654.89 cm^{-1} respectively from Figure 2 and Figure 3 indicated the presence of carboxyl functional group with -C=O stretching.

Stretching	**Wavenumber (cm^{-1})**	
	Figure 2	Figure 3
N-H	3262.04	3402.50
-C=O	1574.09	1654.89

Table 2: Summary of characteristic peaks.

The FTIR spectra obtained from Figure 2 showed all the principal characteristic peaks that were related to diclofenac sodium. Although there was a slight change in the position of the characteristic peaks, there were no disappearance of characteristic peaks of diclofenac sodium from the FTIR spectra of the transdermal film that was formulated with diclofenac sodium and PVP. No chemical interaction was shown when both diclofenac sodium

and PVP were used in effervescent tablet formulation.[23] hence, it could conclude that no chemical interaction took place between diclofenac sodium and PVP when it was formulated as transdermal film.

However, from the results of drug-polymer interaction study using FTIR spectroscopy it was difficult to understand the mechanism of chemical interactions between diclofenac sodium and PVP. Thus, further studies by nuclear magnetic resonance spectroscopy and mass spectroscopy can be used to study chemical interaction between the drug and polymer.

Physical Observations

The observations on the formulated transdermal films could be supported as PVP was freely soluble in methanol and the nature of PVP showed clear in solution.[7] The observations can be supported whereby films obtained from PVP have transparent appearance and in dry form the transdermal films were clear.[11] Hence, formulated films using PVP in this research study showed excellent film-forming properties during fabrication of TDDS.

Thickness

In this experiment, thickness of the film increased with the increased in concentration of PVP. This phenomenon was due to the hydrophilic nature of PVP that absorbs water from the atmosphere that caused increase in thickness of transdermal patches. [24] The results also showed that the thickness of the films was concentration-dependent.[25]

Weight variation

Based on the study, results showed that the weight of the formulated films did not increase proportionally with the increased of PVP concentrations. Even though the concentration of PVP was higher on formulation F3 as compared to formulation F1 and F2, the weight of formulated transdermal films formulated with formulation F3 was lower than the transdermal films formulated with formulation F1 and F2. This was probably due to the variation of temperature and humidity during 24 hours of drying process. This was due to the hydrophilicity nature of PVP that resulted in absorption of water from the air and led to weight variation.[16]

Moisture content

A low standard deviation was observed for formulation F1, which indicated that the films of F1 formulation used for the evaluation did not differ significantly among the three formulated films. Among the six formulations, formulation F6 contained highest percentage moisture content, but the standard deviation was high. This was due to the high concentration of PVP revealed its hydrophilicity nature that absorbs moisture from the air and caused variation of films.[16]

Increased in PVP concentrations would increase the moisture content in the formulation.[26] However, in this study moisture content showed fluctuating trend (Chart 1) when the concentrations of PVP increased. Besides, findings from this study showed that the moisture content was not significantly

different when the concentration of PVP increases. This probably due to the formulated films used for moisture content evaluation were affected by several factors that caused changes on the formulated films. For example, temperature that could bring variability in quality.[27]

Among the six formulations, F5 was the preferred formulation as it had the lowest percentage of moisture content. As low moisture content could ensure the films to maintain appropriate moisture and prevent the films from becoming dried that caused the films became brittle.[28]

Folding endurance

The folding endurance study was important to evaluate transdermal films, as this study was able to identify the capability of the formulated films to maintain its film integrity during skin folding.[29] In this study, transdermal films of formulation F5 had the ability to withstand mechanical pressure along with good flexibility as the mean folding endurance of three formulated transdermal films was more than 150 folds.[25] However, the standard deviation of formulation F5 was the highest among the six formulations. This was due to one of the transdermal film of formulation F5 had the folding endurance of 140 folds. Hence, increase sample size is needed before concluding which formulation of transdermal film exhibits good flexibility.

Formulation F1 had the lowest folding endurance and lowest value of standard deviation as all the three formulated transdermal films formulated by

formulation F1 were broken after 1 fold. This was due to formulation F1 was the thinnest among the six formulations whereby thickness of transdermal film can alter the mechanical strength.[27]

Since there was a significant difference between the concentration of PVP and folding endurance, this finding can be supported, whereby an increase in the concentration of PVP, decrease in the tensile strength. [30] This was due to polymer concentration has a strong effect on the formation of macrovoids.[31] Due to PVP was a water soluble polymer, it caused the higher formation of macrovoids when the concentration of PVP increases and lead to the influence of the tensile strength.[31] However, in this study the folding endurance showed fluctuate results when the concentration of PVP increases. Thus, increase in sample size is needed to further improve the findings.

***In vitro* drug release**

From the calibration graph (Graph 1), a linear relationship was observed as the R^2 was higher than 0.98.[19] This indicated that the absorbance was directly proportional to the concentration. The selection of formulation for dissolution test was based on the folding endurance that was conducted in this research study. Formulation of F4, F5 and F6 were selected, because the formulated films from these formulations had better folding endurance as compared to formulation F1, F2 and F3. Besides, these formulations could be handled without breaking the films during preparation for dissolution test.

Based on the results of *in vitro* drug release, the percentage of drug release increased with the increased of PVP concentrations. This was due to the increases solubility of PVP when PVP concentration increases. [32] Thus, the percentage of drug release increases with the increased of PVP concentrations. The rapid release of the drug was explained as burst effect, where the drug was migrated to the surface of the polymer matrix.[33] The burst effect also could be explained as the surface of hydrophilic drug undergoes rapid dissolution.[29]

The phenomenon of rapid drug released was an advantage in TDDS, as drug that was formulated with PVP can achieve therapeutic levels very quickly and then maintained the drug releases over a period in order to provide sustained release or controlled release of drug.[34] It is important to note that rapid drug release offer the desired effect of localised treatment, because an initial burst release of the drug provides immediate relief followed by prolonged release to promote the gradual therapeutic effect.[35]

Conclusion

In summary, PVP can be used as a film-forming agent in formulating transdermal film as the promising drug release profile was exhibited whereby transdermal films formulated with 8% w/v PVP concentration was preferred in this study as it had the highest percentage of drug release.

Acknowledgement

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Case report

Dens Evaginatus involving multiple primary teeth: A rare case report

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Abstract

This case report describes the anomalous development of Primary maxillary central incisor and mandibular first molars in a two-year-old Chinese boy. The primary maxillary central incisor radiographically demonstrated anomalous development characteristic of dens evaginatus. Similar findings were evident on Primary right and left mandibular first molars. Dens evaginatus is a condition that most commonly exhibited by protrusion of a tubercle from occlusal surfaces of posterior teeth, and lingual surfaces of anterior teeth. Although often observed, these anomalous teeth present some challenges to the dental practitioner. Morphologically anomalous cusp-like protrusions are susceptible to pulp exposure from wear or fracture because of malocclusion, leading to pulpal complications soon after eruption. This article illustrates a case in which a child demonstrated extra cusp in relation to primary maxillary central incisor and mandibular right and left first molars suggestive of dens envaginatus. The many challenges associated with the presence of such teeth are discussed

Keywords: Central incisor, Dens evaginatus, Primary molars, Talon's cusp

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Introduction

Dens evaginatus (DE) is a developmental malformation of crown shape occurring in the early stages of dental development before the mineralization of hard tissues. It is a phenomenon resulting from the outward folding of the inner enamel epithelial layer into the stellate reticulum of the enamel organ and transient focal hyperplasia of the primitive pulpal mesenchyme during the morphodifferentiation stage of the tooth development.[1] This anomaly has more commonly been reported in the permanent dentition with prevalence ranging from 0.06−7.7%. The total number of reported cases in the primary dentition worldwide is only 39 and the affected primary teeth may be maxillary central and lateral incisors and mandibular molars. It occurs in both genders and may be unilateral or bilateral.[2]

Case Report

A two-year-old Chinese boy reported, along with his mother, to the Pediatric dentistry department of Oral Health care Centre, SEGi University, Kota

Damansara, for a routine dental check-up. The child had a normal medical history and his family history was noncontributory. On physical examination, he appeared to be of appropriate stature and weight and in no apparent distress. Intraorally, presence of an extra cusp in the form of a tubercle projecting from the palatal aspect of crown of primary maxillary right central incisor (Talon's cusp) was seen (Figure 1) and also small accessory cusp-like structure-arising from the occlusal surface of the mandibular right and left first molar teeth. (Figure: 2 & 3) Radiographic evaluation of the central incisor revealed an abnormally shaped radiopaque structure composed of normal enamel and dentin and with pulp extension. (Figure: 4)

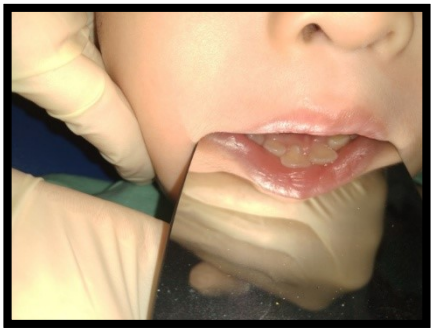
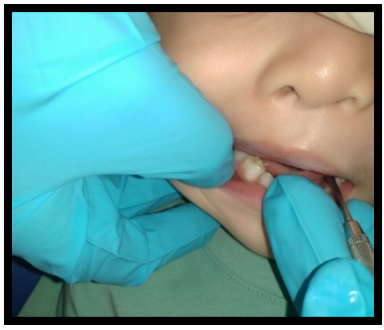


Figure 1: Primary maxillary right central incisor (Talon's cusp)



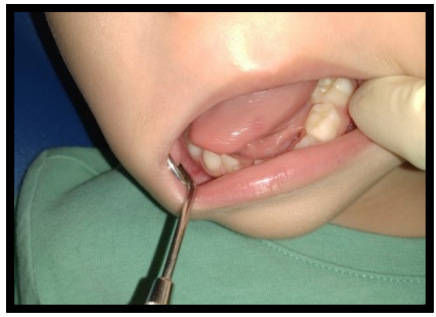


Figure 2 & 3: Primary mandibular right & left first molars

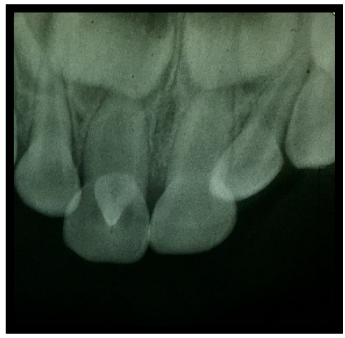


Figure 4: Periapical radiograph of primary maxillary right central incisor (dens evaginatus)

Based on clinical and radiographic examination, treatment plan was discussed the parent. A follow up appointment was scheduled in 3 months. As patient was 2 year old without any symptoms, it was decided to do the trimming of palatal cusp tip (Talon's cusp) after 6 months and follow up for evaluation of mandibular first molars.

Discussion

Dens evaginatus was first described in a human tooth by Mitchell in 1892. The term 'talon' was coined by Mellor and Ripa because of its characteristic resemblance to an eagle's talon in 1970 and this anomaly has been more frequently reported in the Asian population. The first reported case in primary dentition is by Sawyer et al. (1976).[3, 4]

There is a wide variation in the size, shape and location of these anomalies. Due to this variation, accessory cusp found on maxillary or mandibular anterior teeth is often referred to as Talon cusp and accessory cusp which is found on occlusal surface of premolar or molar is referred to as dens evaginatus. The exact etiology of these variations is not clear. However, the probable role of genetics and environmental factors, such as trauma or other local factors affecting the tooth germ have been suggested. Small talon cusps are asymptomatic and require no intervention. Large talon cusps may cause clinical problems including occlusal interference, irritation of the tongue during speech and mastication.[1, 5, 6]

Although it has been mentioned that the occurrence of central cusps in primary dentition is rare but there is no evidence to justify this statement. Most of the reported reviews were on presence of Talon cusps on permanent and primary dentitions and also on dens evaginatus on permanent dentition. Very few cases have been reported on dens evaginatus on primary molars. It is important to monitor regularly, the occlusion during the eruption of tooth with

talons cusp as well as their opposing teeth in order to prevent potential crossbite.[7, 8, 9]

In this present case report, we found that the accessory cusp is centrally situated bilaterally and the cuspal tips extended above the level of adjacent cusps. Based on the clinical presentation, it was assumed that the cause of this formation is similar to dens evaginatus. The bilateral occurrence of these extra cusps along with talons cusp on the palatal aspect of right central incisor is suggestive of dens evaginatus.

Conclusion

Although these additional cusps are rare, their presence may complicate the process of routine oral health care. Generally patients may not report for the treatment of dens evaginatus as it does not present with clinical symptoms always. It is diagnosed either during routine dental checkup or investigating for other complaints. Hence clinician must examine every patient thoroughly so that dental anomalies may be detected early and properly treated. Early detection may reduce the future complications such as cusp fracture, attrition leading to pulp exposure, tongue irritation, damage to periodontium due to excessive occlusal force etc. This patient has been placed under periodic follow up, which includes monitoring of the occlusion and tooth vitality.

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Case report

Immediate implant placement with immediate loading- A case report

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Abstract

Dental implants have provided an excellent treatment option to restore edentulous spaces. Successful formation of a direct bone to implant interface is the goal in implant therapy. Immediate loading is an alternative to the two-stage surgical procedure. Improved surgical instrumentation, implant design and surface topography, changes the concept of a two-stage surgical procedure to a one stage procedure. Early and immediate loading of dental implants can significantly decrease the treatment time and thus result in an increase in patients' comfort**.** This case report describes the placement of implants in fresh extraction sockets in the mandibular anterior region and immediately loading them with a provisional bridge**.**

Keywords: Implants, surgical procedure, bone, edentulous spaces

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Introduction

Dental Implants have been one of the most utilized treatment options of modern dentistry. The advancement attempts made in implant dentistry from its infancy have been aimed at providing success in three main aspects – functional stability, biological stability and esthetics.[1] Healing following a tooth extraction often leads to alveolar bone atrophy.[2] Changes in the alveolar bone dimension are more pronounced during the first six months of extraction followed by a slow resorption rate thereafter.[3] Immediate implant placement helps to prevent this post extraction alveolar atrophy.[4] The concept of placement of an implant immediately in fresh extraction socket was described by Schulte and Heimke in 1976, however recently this concept has been explored and utilized more often.[5] This concept also has the added advantage of reducing the number of surgical steps, treatment time and preserving the alveolar bone and facilitating better esthetic outcomes.[6] However, this treatment concept cannot be applied to all dental implant cases but only to cases where it is indicated. Another additive to this concept of immediate implant placement is immediate loading which refers to the immediate prosthetic loading: the placement of a temporary restoration immediately after the insertion of the fixture (within 48–72 hours after surgery). This approach provides an aesthetic benefit to the patient, who can avoid wearing uncomfortable removable dentures during the healing period. The placement of an immediate provisional restoration also provides better esthetics with respect to gingival tissues, which can be modeled around it immediately.[7]

The following case report describes a case of immediate implant placement along with immediate loading using provisional restoration.

Case – report

A 32-year old healthy male patient presented to the dental clinic with the chief complaint of mobility in his lower front tooth region. Patient's medical history was non-contributory. He had noticed the mobility since past 3 months and reported an increase in it over these months. On clinical examination, there was presence of plaque and calculus (score of 2). Grade III mobility with relation to 31,32,41,42 was seen. Miller's class III gingival recession with respect to 31,32,41,42 (Figure 1). There were generalized probing pocket depths of 4 to 6mm. Trauma from occlusion was absent. Temporomandibular disorders or parafunctional habits were absent. Radiographic examination revealed extensive bone loss with respect to 31,32,41,42. A diagnosis of generalized chronic periodontitis was made based on clinical and radiographic findings. After appropriate treatment planning, immediate implant placement with respect to 42 and 32 using endo-osseous self-tapered root form implant (Myraid, Equinox, Netherlands) in phase two of the treatment plan was planned. Patient had also insisted about his esthetics after implant placement. Hence, considering the patient's need, an immediate temporization of the implants was also planned in the same visit.

Pre-surgical radiographic evaluation was carried out with radiovisiography (RVG), panoramic radiograph for appropriate treatment planning (Figure 2).

Systemic examination of the patient revealed no abnormality and routine blood investigations were carried out to exclude any complications.

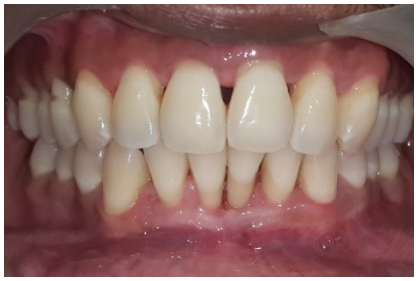


Figure 1: Pre-operative implant site

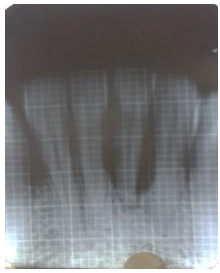


Figure 2: intraoral periapical radiograph of lower interiors

The pre-operative clinical and radiological examinations were undertaken for assessing the length of existing retained root in order to determine the length of future implant and width of socket. Before proceeding with the implant placement, the patient signed an informed consent form. The surgical procedure for immediate implant placement began with the administration of the nerve block in the treatment area using 2 percent lignocaine with adrenaline 1:80000 (Lignox 2% A, Indoco Remedies Ltd, Mumbai, India) to anesthetize the surgical site. A sulcular incision was given using no.15 blade and a full thickness mucoperiosteal flap was raised (Figure 3).

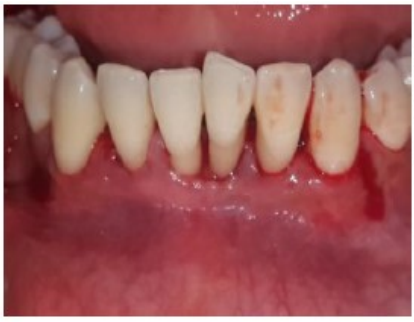


Figure 3 - Sulcular Incision given

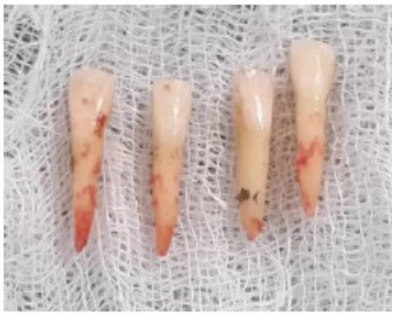
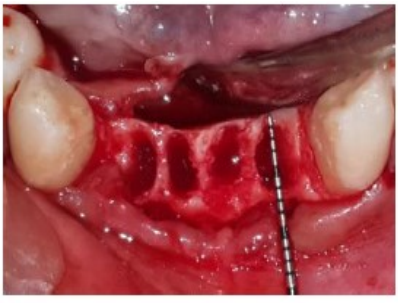


Figure 4 - Extraction of 31, 32, 41 42

Following which 31,32,41,42 were extracted atraumatically using a periotome and periosteal elevator (Figure 4). The resultant extraction socket was checked for any osseous defects. All four walls of the extraction socket were found to be intact. The socket was cleaned of any granulation tissue present (Figure 5).



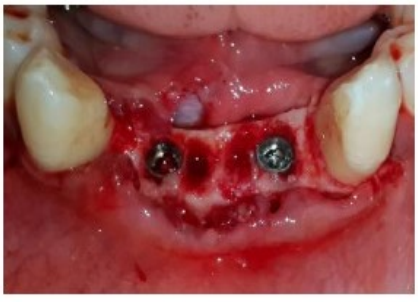


Figure 5 –Resultant extraction sockets Figure 6 - Following implant placement

The osteotomy procedure was initiated using the pilot drill engaging the apical bone in the socket and an IOPA was taken with the paralleling pin to check for the implant angulation (parallelism) in the region of 32 and 42. Sequential

drills were then used as per the implant system guidelines to place an implant of 3.3 X 13mm (Myraid, Equinox, Netherlands) in the region of 32 and 42 and an implant insertion torque of 35N was achieved manually (Figure 6). Standard straight implant abutments were placed (Figure 7).

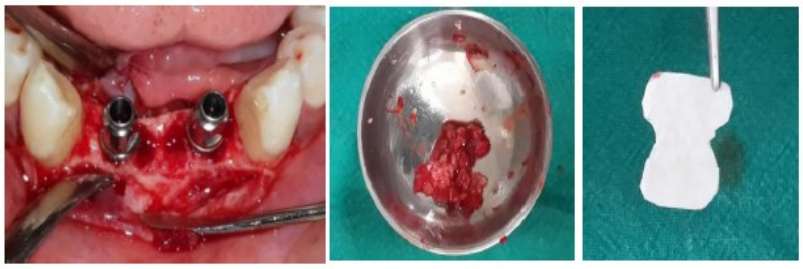


Figure 7-Straight Abutments placed & Autogenous bone graft and demineralized bone graft for socket grafting with respect to 31, 41 & collagen membrane

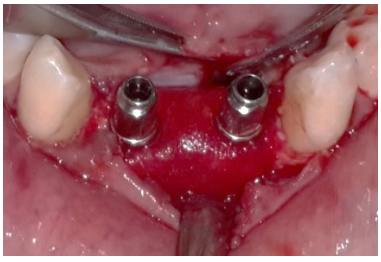


Figure 8 - Grafting done and GTR barrier membrane placed

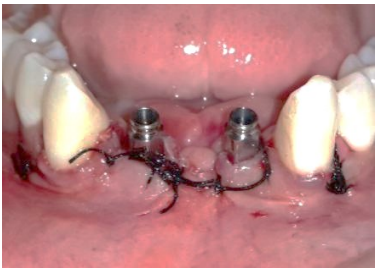


Figure 9 - Sutures given

The resultant sockets of 31 and 41 were grafted using demineralized bone allograft and autogenous bone graft and bioresorbable collagen GTR membrane (Bio-Guide, Geistlich Pharma AG, Wolhusen, Switzerland) was placed (Figure 7). Simple interrupted sutures were placed using 3-0 silk suture

to approximate the flap (Figure 8,9). For immediate temporization, an elastomeric impression was made. An acrylic provisional bridge was fabricated and cemented in the same appointment (Figure 10).

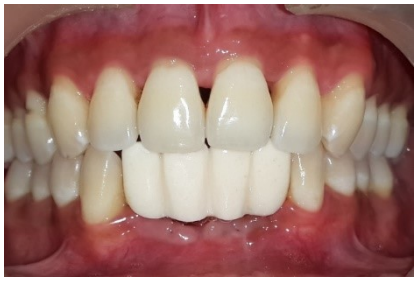


Figure 10- Two weeks post-operative

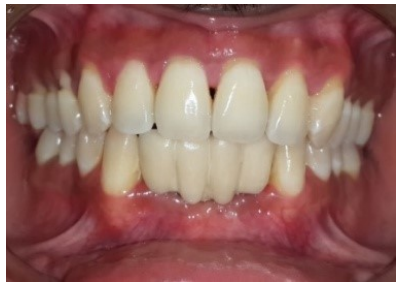


Figure 11 - Final prosthesis placed

Care was taken to prevent any incisal contact of the provisional prosthesis during centric or lateral excursive moments. Post-operatively, an antibiotic (amoxiclav 625 mg, 2 times daily for 5 days) and an analgesic (ibuprofen 400 mg, every 8 hourly for 3 days) were prescribed and post- operative instructions were given. 0.12% chlorhexidine gluconate mouthwash was prescribed for 7 days post-operatively. Patient was advised not to bite using the temporary prosthesis for 6-8 weeks and was asked to report back after 7 days for suture removal. The acrylic provisional prosthesis was replaced by porcelain fused metal crown after the fourth month follow-up showed good soft tissue contours clinically and hard tissue stabilization radiographically (Figure 11).

Discussion

Immediate implant placement with immediate loading is one of the most popular treatment options in implant dentistry. However, for its success it is vital to consider various factors like socket anatomy, implant positioning, jumping distance, type of provisional restoration.[8]

The pre-operative factors affecting the outcome of immediate implant placement is the socket anatomy, presence or absence of infection at the site and gingival biotype.

Type I socket described by Ellen and Tarnow [9] is the ideal socket type for immediate implant placement, which was also present in this case (figure 5).

A systematic review by Lee *et. al*. stated that implants can be placed in infected extraction sockets after thorough socket debridement. However, to achieve good aesthetic outcomes the width of keratinized gingiva should be considered while attempting immediate implant placement in infected sites.[10]

Another approach which can be utilized while placing immediate implant is use of flapless surgery which provides the added advantage of improved esthetic outcomes and less soft and hard tissue loss due to its minimal invasive property. However, when in doubt regarding the space between the implant fixture and socket wall referred as jumping distance, raising a flap is always advisable. A randomized controlled trial by Jane et al. concluded that both flap and flapless procedures have high success in implant dentistry However, while attempting a flapless technique patient must be properly selected.[11]

Various studies suggest that if the jumping distance is less than 2 mm, then no regenerative therapy is needed for filling this gap. If, however the distance is more than 2 mm, then it is recommended to use a regenerative therapy using bone graft and GTR membrane which requires raising of a full thickness mucoperiosteal flap as done in this case.[12]

The finishing of the provisional restoration also plays an important role to achieve good soft tissue contours post healing. The contours and optimum polishing are one among the important factors to be considered while designing a provisional restoration.

To achieve predictable and desirable outcomes with immediate implant protocols, it is important to adhere to advanced surgical skills, ideal extraction socket conditions and knowledge of local anatomy.[13] It is recommended that when ideal conditions are not present, other implant placement timing protocols that provide good clinical outcomes with regards to soft and hard tissues be followed.

Conclusion:

Appropriate surgical treatment, restorative procedures, and clinical experience are essential when performing immediate placement of implants with immediate loading. Immediate implant placement following tooth extraction might be a viable alternative to delayed implant placement. However, it requires careful case selection and a specific treatment protocol, proper case

selection, diagnosis and treatment planning, meticulous post-operative care preceded by a good surgical and prosthetic protocol to ensure the long-term success of the immediate implants. Also, it should not be used as a universal approach but only in cases where the outcomes can be predicted.

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- **Conclusion**

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- *Journal:* Suresh KV, Shenai P, Chatra L, Ronad YAA, Bilahari N, Pramod RC, et al. Oral mucosal diseases in anxiety and depression patients: Hospital based observational study from south India. J Clin Exp Dent. 2015; 7:95–99.
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