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Content

Letter to editor

I am a general dentist: Why is screening of obstructive sleep apnea in chronic kidney disease patients my concern?

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Dear Editor,

Obstructive sleep apnea (OSA) is characterized by upper airway collapse while sleeping at night. There is an increasing body of evidence that links OSA with chronic kidney disease (CKD).[1,2] Though this combination is seen commonly in this patient group, documented current global evidence ends with a note stating under-diagnosis of OSA.[1]Family physicians (FP) are the front-liners to identify the disease and serving their best. In such circumstances, why is screening of OSA in CKD patients', a general dentist's (GD) concern? Readers could raise the question that dental considerations for sleep apnea would be sufficient to elucidate this scenario? Given yes would mislead the title and not

to get confused with the sleep apnea considerations in dental offices. The core discussion is about why a GD should screen OSA and most importantly why is it compulsory in CKD patients, rather than the diagnostic methods?

The first reason is that GDs equally have opportunities like FPs to diagnose OSA during their routine practice. Interestingly, dental findings suggest that dentists could be better diagnosticians for OSA than the specialized physicians considering the two main visible signs of this disorder: enlarged tonsils and tongue, which are easily noticeable during dental care.[2] In addition, recent reports express that neck circumference >40cm, large tongue, Mallampati score of Class 3,4 and deep palatal vault as independent predictors in high-risk OSA patients.[3] Therefore, CKD and OSA despite sharing the common risk factors such as obesity, hypertension, smoking, and alcohol, the mentioned intra-oral and extra-oral signs can aid the dentists in diagnosing OSA before CKD is reported. This indeed increases the confidence of a GD.

Secondly the current knowledge in the medical field suggests a potential bidirectional association between CKD and OSA.[4,5] The mechanism suggests that CKD patients often carry excess fluid that can lead to upper airway narrowing. The fluid overload often leads to interstitial pulmonary edema causing central apnea, which could be responsible for the OSA. The similar pathophysiology of both the diseases increases the possibility of them to be possible risk factors for each other.[4] Therefore, OSA may be consequent to and aggravate CKD progression. OSA

appears as a potential trigger and mandatory that GDs understand the seriousness of comorbidities.

Thirdly, 80% of the moderate and severe cases remain undiagnosed according to American Sleep Association.[2] A recent exhaustive meta-analysis undertaken by Voulgaris A and team showed that prevalence of moderate and severe OSA in CKD patients was 34% and 37% respectively.[5] Indeed true that GD potentially sees their patients more frequently than physicians, especially those who regularly visit for a routine check-up. Given such an opportunity in dental practice should be utilized to identify the undiagnosed OSA in CKD patients. The good news is that the identification and treatment of OSA may lead to an intervention considerably delaying the progression of kidney disease.[5,6]

The health of the CKD population is facing a new threat (risk factor) every day and OSA is one such. It is emphatic to GDs to welcome new perspectives wherein compulsory screening for OSA as a part of comprehensive medical and dental history, focusing on the existence of the bidirectional association between CKD and OSA would help the patients to receive the most effective care. In the patient's best interests, prioritize them as high-risk candidates based on the associated risk factor and mutually refer to sleep physicians. It's in good belief that increasing basic science and clinical medicine courses in dental schools would help the dentists to become oral physicians and provide an opportunity to participate in major reform of the health-care system.

Conflict of Interest: None Declared

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Review

Association of air pollution and hospital admissions due to exacerbation of chronic obstructive pulmonary disease in Asia: A scoping review

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Abstract

Background: Air pollution is highly associated with health-related problems. Particulate matters (PM) such as PM10, PM2.5, nitrogen dioxide, sulfur dioxide, carbon monoxide and ozone levels are associated with exacerbation in chronic obstructive pulmonary disease patients. This review aims to identify the relationship between air pollution and the rate of hospitalisation due to exacerbation of chronic obstructive pulmonary disease in Asia.

Methods: A scoping review was performed using the method of Arksey and O'Malley.–Systematic searching of articles was conducted from PubMed and ScienceDirect. Articles were only included if they reported on the association between exacerbation of chronic obstructive pulmonary disease and hospitalisations among adults aged 18 years and above in Asian countries.

Results: 65 articles were retrieved from two search engines. Eight articles met the inclusion criteria for review. Most of the studies have shown linear correlation between PM2.5 and acute

exacerbation of chronic obstructive pulmonary disease hospitalisations. Three studies have shown that there is a significant association between PM10 and acute exacerbation of chronic obstructive pulmonary disease, while four studies have proved that there is positive correlation between PM2.5, nitrogen dioxide, sulfur dioxide, carbon monoxide and acute exacerbation of chronic obstructive pulmonary disease hospitalisations. Four studies had also concluded that female patients and older patients are more susceptible to acute exacerbation of chronic obstructive pulmonary disease hospitalisations.

Conclusion: Particulate matters such as PM2.5, PM10, nitrogen dioxide, sulfur dioxide, carbon monoxide, ozone, as well as female gender and old age is highly associated with hospital admissions due to acute exacerbation of chronic obstructive pulmonary disease cases in Asia.

Keywords: Air pollution, Asia, COPD, exacerbation, and hospitalisation

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Introduction

Air pollution is a phenomenon that has happened for a long time across the world and it brings a lot of problems to us especially health related problems.[1] Air pollution refers to the release of pollutants into the air that are detrimental to human health and the

planet as a whole.[2] The condition of air pollution has become more and more severe compared to decades ago, and we as human beings who are affected by this problem, need to pay more attention to this problem.[3]

There are various types of pollutants that have been released into the atmosphere and cause air pollution, for example nitrogen dioxide, sulfur dioxide, carbon monoxide and so on.[3,4] Human activities are the main source of these pollutants such as emission from factories, wastes emitted from vehicle, construction and agriculture activities.[3–5] Some pollutants are also contributed from indoor air pollution such as secondary smoke from smoking cigarettes, emission from air conditioning, smoke from cooking and burning of coal. Besides all those pollutants mentioned above, PM10 and PM2.5 forms of pollutants are the most harmful pollutants to human beings. PM10 and PM2.5 are particular matter with diameter less than 10 and 2.5 micrometer.[6] For PM2.5 pollutants, it is mainly emitted from combustion of gasoline, oil, diesel fuel and wood while for PM10 pollutants are come from dust in construction sites, landfills and agriculture.[7]

The most common health issue related to air pollution are respiratory related diseases such as asthma, chronic obstructive pulmonary disease (COPD) and respiratory disease.[8] This is because these particular matters are able to pass through our pulmonary protective system and reach to the very deep side of lungs.[9] With the increase in severity of air pollution, cases of respiratory infection such as influenza and bacterial pneumonia are increasing.[10] As people with pulmonary disease have a higher

risk than normal healthy people to get affected by air pollution,[11] a scoping review was done to understand how the air pollution is associated with hospitalisation due to exacerbation in COPD patients.[12]

Methods

A scoping review was conducted on the association of air pollution and hospital admissions due to exacerbation of COPD patients in Asia. A 6-step methodological framework that was developed by Arksey and O'Malley was defined for the review[13]. However, in our scoping review, only steps 1 to 5 of the framework were defined. The structure of the framework was outlined in the following manner:

1) Identification of the research question.

2) Identification of relevant studies.

3) Selection of studies for review.

4) Charting the data.

5) Collating and summarizing the results

Step 1: Identification of the research question

The research question is "What is the association of air pollution and hospital admissions due to exacerbation of chronic obstructive pulmonary disease in Asia?"

Step 2: Identification of relevant studies.

A search strategy was conducted according to the Preferred Reporting Items for Systematic and Meta-Analyses (PRISMA) Statement Protocol as figure 1. The electronic database, Pubmed and ScienceDirect were utilised mainly to identify, define, and recognize the available potential pieces of literature present that were associated with air pollution and hospital admissions due to the exacerbation of COPD patients throughout Asia. Through this, a Boolean strategy was implemented for further effective searching by using combined keywords to locate the relevant studies based on the stated review. The combined keywords used were "air pollution AND hospitalisation AND exacerbation AND COPD AND Asia" for both Pubmed and Science Direct. Through this search, a total of 65 articles were obtained, 29 of which were from the Pubmed database, and the remaining 36 from Science Direct. Table 1 shows the words used on the PubMed search strategy on hospitalisations due to AECOPD from air pollution.

Step 3: Selection of studies for review.

The selection of 8 relevant articles out of 65, pertaining to air pollutants associated with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), was based on the following inclusion and exclusion criteria.

Inclusion criteria: Studies that were related to hospitalization due to the exacerbation of COPD cases from air pollution in Asia involving adults aged 18 years and above in Asia.

Exclusion criteria: Studies that were not done in English, articles with irrelevant or inadequate information, were excluded.

Step 4: Mapping the data

Among the 8 selected qualitative studies, details and data obtained were mapped out and tabulated. This tabulation comprised of authors, years of publication, the aim of the study, country or region of study, characteristic of studies, design or methodology and key findings of each relevant articles. The summary of air pollutants associated with AECOPD among eight qualitative studies can be observed in (Table 2).

Step 5: Collating and summarizing the results

The acquired evidence was collated, summarized, and reviewed thoroughly throughout the entire process.

Results

A total of 65 articles were retrieved from two databases which are PubMed and ScienceDirect, however, there are 2 duplicated articles. Thus, 63 articles were left for title and abstract screening. After the primary screening, 15 articles were chosen for full text screening. A total of 7 articles were excluded with due to language barrier and inadequate information. Lastly, 8 qualitative studies met our inclusion criteria, key concepts, and theme of our research question. These studies were conducted in China or Korea. The different study cities from China that are being investigated include Jinan, Shijiazhuang, Shanghai, Yancheng and Beijing. The steps and summary of the studies were shown clearly with the PRISMA diagram in figure 1 and table 2, respectively.

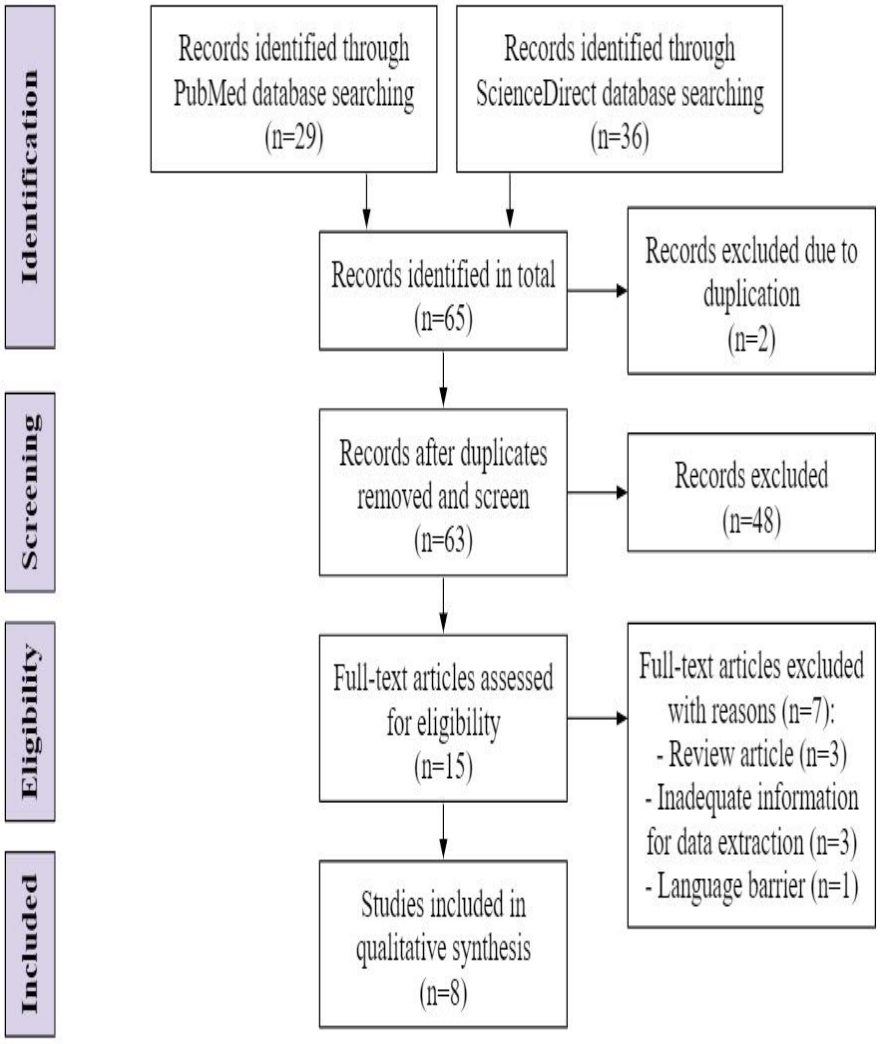

Figure 1 - PRISMA diagram in the selection of articles for scoping review

Table 1 – Summary of words used on PubMed as a search strategy

Concept	Keyword	MeSH
Air pollution	Air pollute*	Air pollution [MeSH Terms]
Hospitalisation	Hospital*	Hospitalization [MeSH Terms]
Exacerbation	Exacerbate*	-
Chronic obstructive pulmonary disease		pulmonary disease, chronic obstructive [MeSH Terms]
Asia	Asia*	Asia [MeSH Terms]

PM2.5 and PM10 associated with AECOPD hospitalisations

Six out of the eight qualitative studies have reported a linear correlation between PM2.5 and AECOPD hospitalisations.[14–19] In the six studies, all of the studies have concluded that the rate of AECOPD hospitalisations increased when the concentration of PM2.5 increased in the short-term period. Three out of the six studies have shown that there is a significant association between PM10 and AECOPD.[15,16,20]

NO_2, CO, SO_2 and O_3 associated with AECOPD hospitalisations

Five studies have investigated the relationship between NO_2, CO, SO_2 and O_3 with AECOPD hospitalisations.[15,19] Four out of these five studies reported that there is a strong positive correlation between PM2.5, NO_2, CO, SO_2 and AECOPD hospitalisations, but showed a negative correlation with O_3 level.[16–19] According to Liang et al., PM2.5, PM10, NO_2 and CO demonstrated a positive correlation to each other but showed a moderate positive correlation with SO_2.[15] Besides that, it was also mentioned that AECOPD hospitalisations can be increased when exposure to O_3, during the warm season and decreases AECOPD hospitalisations by increasing with O_3 exposure during the cold season.[15]

Gender and age associated with AECOPD hospitalisations

There are five studies which discussed association of gender and age with AECOPD hospitalisations.[15–18,21] Chen et al. has reported that male patients are more sensitive to air pollutants and have a higher risk of AECOPD hospitalisations.[21] On the other hand, another four studies had concluded that female patients and older patients are more susceptible to AECOPD hospitalisations.[15–18] Out of these four studies, Xu et al. reported that females aged 60 years and above are at high risk of AECOPD hospitalisations.[18] Liang et al. reported on females aged 65 years and above while Sun et al. has recorded that females aged more than 75 years are most susceptible to AECOPD hospitalisations.[15,17] Qu et al. also mentioned that retired female patients are at high risk in AECOPD hospitalisations.[16]

Table 2 - Summary of air pollutants associated with AECOPD among eight qualitative studies

No	Authors/ year of publication/ origin	Aim of the study	Country/ region of the study	Study characteristics	Design/ methodology	Key findings
1	Chen et al. 2018 China[21]	To study the short-term effects of air pollution on the hospitalisation rates of the individual with AECOPD, stroke, myocardial infarction (MI) in Jinan, China	Jinan, China	Population from Jinan Qilu Hospital, Provincial Hospital of Shandong Province and Central Hospital of Shandong Province. Inclusion: (1) ≥18 years old (2) resided and worked in the study area (Jinan City) during the study period	Observational study for 3 years	(1) Male patients aged ≥ 65 years were more sensitive to air pollutants and were at higher risk of hospitalisation for AECOPD. (2) PM2.5 and daily exposure to SO_2 and NO_2 can lead to cardiovascular disease and affect the admission risk of stroke patients. (3) SO_2 has an adverse impact on the admission of individuals with MI.
2	Qu et al. 2019 China[16]	To analyse the relative cumulative risk factors from air pollution associated with AECOPD under exposure to high pollution levels and calculate the attributable percentage of AECOPD in Shijiazhuang, China	Shijiazhuang, China	Population from Health Insurance Center of Shijiazhuang City, Hebei Province and electronic medical records of all primary and secondary discharges diagnose as AECOPD patient from tertiary and secondary hospitals. Inclusion: (1) primary diagnosis of	Time-series study for 4 years	(1) A linear positive relationship between AECOPD and PM2.5, PM10, NO_2, CO and SO_2. (2) A negative linear correlation between AECOPD and O_3. (3) Every increase of 10 μg/m3 in PM2.5, PM10, SO_2 and NO_2 level were associated with 1.1%,

				AECOPD and defined according to the ninth version of International Classification of Diseases (ICD-9) (2) resided at urban area of Shijiazhuang (3) patient with AECOPD from tertiary and secondary hospitals (4) ≥ 35 years old		0.4%, 0.3% and 1.6% increases in COPD hospitalisation, respectively. Every increase of 0.1 mg/m^3 of CO levels, it increases 0.5% of hospitalisation. (4) Short-term exposure to high concentrations of PM significantly increased the daily rates of AECOPD hospitalisation. (5) PM2.5, PM10, NO_2, CO caused the significant burden of AECOPD hospitalisation in Shijiazhuang, China. (6) The risk of female and retired patients is higher.
3	Wang et al. 2015 China[20]	To investigate the Geographical Information System (GIS) based on the spatial relationship between ambient air pollution and AECOPD hospitalisati	Jinan, China	Population from five large-scale hospitals in Jinan. Inclusion: (1) AECOPD hospitalisation and identified by ICD-10 (2) resided and worked in Jinan City during the	Generalised linear model (GLM) for 1 year	(1) PM10 has the greatest spatial correlation with AECOPD hospitalisation in the workplace. (2) SO_2 has the greatest spatial correlation with AECOPD hospitalisatio

		on in Jinan, China		study period (3) >18 years old		n in the residence. (3) Every 10 $\mu g/m^3$ increase of PM10 at the workplace, it increases 7% of AECOPD hospitalisations.
4	Zhang et al. 2018 China[19]	To study the association between various air pollutants and hospitalisations of various specific respiratory disease and medical expenditure for these diseases in Shanghai, China	Shanghai, China	Population from XinHua hospital in Shanghai. Inclusion: (1) resided and living in Shanghai (2) primary diagnosis with five independent respiratory diseases which is pediatric respiratory disease (PRD), upper respiratory infection (URI), lower respiratory infection (LRI), asthma and COPD	Time-series study for 3 years	(1) It showed a significant relationship between PM2.5, CO, SO_2 and NO_2 level with PRD and URI visits along with 128-352 CNY and 332-467 CNY per IQR increments in air pollutants, respectively. (2) A significant association between PM2.5 and O_3 with COPD visits by 432 and 774 CNY respective per IQR increments. (3) Non-significant association between all pollutants with asthma and LRI.
5	Jo et al. 2018 Korea[14]	To investigate the effect of PM2,5 and its chemical constituents on AECOPD	Chuncheon, Korea	Population in Chuncheon, Gangwon-do from Korean National Health	Time-series study for 6 years	(1) Hospital admissions were not affected by an increase in PM2.5 concentration.

		hospital visits in Chuncheon, Korea.		Insurance Service (KNHIS). Inclusion: (1) according to ICD-10 code (2) all-age		(2) As PM2.5 concentration increases, the outpatient visit and total hospital visits increase. (3) Chemical constituents of Mg, Al, Si, Ti, As, Br and elemental carbon were having a high risk of AECOPD hospitalisation in males only.
6	Xu et al. 2016 China[18]	To explore the association between PM2.5 pollution and hospital emergency room visits (ERV) for total and cause-specific respiratory diseases in urban areas in Beijing, China.	Beijing, China	Population from ten general hospitals located in urban areas in Beijing. Inclusion: (1) according to ICD-10 code (2) diagnosis with total respiratory diseases which included upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), AECOPD and asthma	Time-series study for 1 year	(1) Every 10 $\mu g/m^3$ increase in PM2.5, it increases ERV of 0.19% for URTI, 0.34 % for LRTI and 1.46% for AECOPD. (2) No significant association between PM2.5 and asthma. (3) PM2.5 was strongly correlated with SO_2, CO and NO_2 but negatively correlated with O_3. (4) PM2.5 more affects females and people $\geq$ 60 years old.
7	Sun et al. 2018 China[17]	To study the association between PM2.5 and AECOPD in	Yancheng, China	Population from Yancheng First People's	Time-series study for 3 years	(1) A positive and significant relationship between

		Yancheng, China.		Hospital and Third People's Hospital. Inclusion: (1) according to ICD-10 code (2) diagnose with AECOPD		short-term exposure to PM2.5 and AECOPD hospitalisation. (2) A 10 μg/m^3 increase in PM2.5 was associated with 1.05 % increase in AECOPD. (3) Among the population, females and people aged > 75 years old are at higher risk. The cold season also represents a higher risk in AECOPD hospitalisation. (4) Relationship between PM2.5 and AECOPD was robust after controlling O_3 level but decreased after controlling NO_2, SO_2 and CO levels.

8	Liang et al. 2019 China[15]	To investigate the associations between the number of cases of AECOPD advanced by air pollution each year in Beijing, China.	Beijing, China	Population from the hospital discharge database operated by the Beijing Public Health Information Centre. Inclusion: (1) according to ICD-10 code (2) primary discharge diagnosis of AECOPD (3) ≥18 years old	Time-series study for 5 years	(1) Total of 161613 of AECOPD hospitalisation cases, with most males patients and people aged ≥ 65 years old. (2) Reduction risk (RR) of AECOPD hospitalisation per IQR increase in pollutant was 1.029. (3) Increase with O_3 exposure, it significantly increases AECOPD hospitalisation during the warm season and decreases hospitalisation during the cold season. (4) PM2.5, PM10, NO_2 and CO showed a positive correlation to each other but showed a moderate positive correlation with SO_2. (5) Women and aged 65 years or older were most susceptible.

Discussion

All the studies have reported significant association between the atmospheric PM and AECOPD. Majority of the studies (6 out of 8) have concluded that PM2.5 has caused a higher prevalence of

AECOPD hospitalisation[14-19] while three studies found out a significant association between PM10 and AECOPD hospitalisation.[15,16,20] PM10 are usually trapped in the upper airway after being inhaled. However, PM2.5 may be able to approach the bronchioles and alveolar spaces.[22] Furthermore, water-soluble pollutants can enter the systemic circulation through the alveolar capillaries.[22] Subsequently, this activates the inflammation on the epithelial cells.[23] Besides, the particulate matters may also increase oxidative stress.[23] Thus, this may aggravate underlying pulmonary disease such as COPD. Toxicological studies have proposed that acute impairment of the lung cellular defence is also one of the causative factors that contribute to the exacerbation of COPD.[24] The hospitalisation rate was also found to be increased when the PM2.5 increased by every 10 $\mu g/m^3$.[18]

Increment of gaseous pollutants such as NO_2, CO, SO_2 and O_3 in the atmospheric air were found to have a strong association with AECOPD hospitalisation. Qu et al reported that the relative risk of NO_2 - associated AECOPD hospitalisation is the greatest.[16] However, Wang et al and Xu et al have recorded that SO_2 has a greater association with AECOPD hospitalisation.[18,20] This may be caused by exhaustion of air pollutants from heavy industries in the area associate with the combustion of fossil fuels including sulfur.[25] According to a statistic from World Health Organisation (WHO), there are approximately 1.6 million death due to exposure of solid fuels per year.[26] Of these, approximately 6930000 cases are associated with COPD.[26] The exposure to SO_2

was found to be associated with respiratory symptoms such as wheezing and shortness of breath.[25] This in turn increases the risk of exacerbation of previously occurred respiratory disease such as COPD.[27] In contrast, the implementation of Air Pollution Prevention and Control Action Plan (APPCAP) in Beijing has greatly reduced the SO_2 concentration.[15] Furthermore, it is found that increased amount of NO_2 and SO_2 causes the inflammation of the epithelial cell as they act as an irritant due to their property as high reactive oxidant.[28]

Most of the studies did not find any correlation between O_3 exposure and hospital admission due to AECOPD.[16–19] However, there were approximately 254,000 deaths from COPD which were attributable to O_3 in 2015.[19] A causal link was found between increased COPD mortality and long-term exposure to ozone.[19] There is a large body of evidence that links the ozone exposure mortality to the adverse effects on the human respiratory system. This includes significant changes in structure and function of lungs in humans and increased morbidity and mortality from COPD, especially during warmer seasons.[29] In the study by Liang et al, they have noted that there is a positive association during warm seasons.[15] Nevertheless, the seasonal effect of O_3 on AECOPD is unclear. It can due to the behavioural pattern of the people during different seasons. For instance, people tend to open the window or attend outdoor activities more frequently when the weather is hot. This indirectly increases their exposure to the polluted air. In another way, most people may stay indoor during cold seasons. Therefore, the exposure to O_3

decreases significantly and the rate of AECOPD hospitalisation declines. However, it may be different in people in Yancheng, China where the condition is the opposite and exacerbation is higher during cold seasons according to Sun et al.[17]

Liang et al observed that there is a 3% increase in acute exacerbations of COPD per 1 mg/m³ increase in CO.[15] However, two studies from Shang Hai[30] and Hong Kong[31] reported that low concentration of CO is negatively associated with the exacerbation of COPD. Both authors suggested that this may relate to the anti-microbial activity and anti-inflammatory properties of low concentration CO. Nonetheless, there are only a few studies available from Asia that are investigating the relationship of CO and AECOPD. Therefore, more studies are needed to confirm the association of AECOPD and CO in ambient air pollution. In studies in Europe and North America, it is found out that there were stronger association between hospitalisation due to AECOPD and CO pollution in ambient air. A possible explanation is that may be due to the difference of the concentration of ambient CO.[32]

In the study by Chen et al., the authors have analysed that elderly aged 65 years and above has a higher risk of hospitalisation due to AECOPD. They were also found to be more sensitive to air pollutants when compared to females aged below 65 years old. The prevalence of AECOPD in male is higher than females in China. This is due to a higher smoking rate of males in China. Approximately 74% of male that is older than 35 years old in China smoke.[33] Age is also one of the factors for hospital

admission due to AECOPD. As age increases, one is more vulnerable to the exposure of PM2.5, PM10, SO_2, NO_2, and CO. For instance, Qu et al noted that retired individuals were more likely to experience AECOPD. This may be due to weak immune systems, decline of respiratory system function or other comorbidities. As a result, weakened immune function, poor lung function, higher prevalence of COPD and increased sensitivity to air pollutants can be an underlying reason of AECOPD in elderly aged 65 years and above.[34]

Sun et al have found out that there is a large association between female patients and PM2.5 in ambient air. Besides, Qu et al. and Xu et al. have also noticed that females are more susceptible to the effects of PM2.5 compared to male.[16,18] It is suggested that it may be due to the physiological difference between male and female. For instance, the size of the airway where male have larger airway compared to female.[35] Jo et al. have also explained that the difference in gene expression of male and female should also be considered.[14]

Conclusion

In the nutshell, the increased amount of PM in the atmosphere increases hospital admissions due to AECOPD. Other gaseous pollutants such as NO_2, CO, SO_2 and O_3 in the atmosphere also contribute to AECOPD but not as much as PM. Factors such as the old age and female gender are also associated with increased AECOPD hospitalisations from air pollution.

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Original article

Factors affecting self-efficacy and the effects of self-efficacy on academic achievements among medical and health sciences students at a Malaysian private university

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ABSTRACT

Background: Self-efficacy refers to ones' beliefs in his or her own ability to perform and complete novel tasks or to cope with adversity in challenging situations. It is an important aspect of the self-concept and has been linked to the one's academic achievement, life satisfaction and self-esteem. The present study aimed to investigate the interdisciplinary differences in general self-efficacy (GSE) among medical and health sciences students at SEGi University, Malaysia. The effects of demographic factors on GSE, as well as the effects of GSE on the students' academic achievements were also explored.

Materials & Methods: This was a cross-sectional study involved 86 medical, 81 dental and 64 optometry Year 1 and Year 2 students at a Malaysian private university. The General Self-

Efficacy Scale (GSES) was used to assess the GSE of the participants. Analysis of data was carried out using the Statistical Package for the Social Sciences (SPSS) software version 22. Analysis of Variance (ANOVA) and t-test were used for comparisons of means. Relationship between two continuous variables was determined using Pearson's correlation. A p value of <0.05 was considered statistically significant.

Results: Findings showed significant interdisciplinary differences in mean GSE scores among medical, dental and optometry students. Various demographic factors were observed to play a role in the GSE of the students. However, the GSE of high achievers and non-high achievers did not differ significantly.

Conclusions: Age, gender, nationality, family income and the type of course and accommodation of students were factors affecting the GSE, but GSE had no significant influence of the academic achievements of students.

Keywords: Self-efficacy; interdisciplinary differences; medical students; health sciences students; academic achievements

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Introduction

Perceived self-efficacy is defined as "people's beliefs about their capabilities to produce designated levels of performance that

exercise influence over events that affect their lives". According to Bandura, there are four sources of self-efficacy information: 1) mastery experience, 2) verbal persuasion, 3) vicarious experiences and 4) physiological states.[1] In the first, one's previous successes or failures shape one's beliefs about one's ability, whereas in the second, one is verbally persuaded concerning his or her competence by others. Thirdly, vicarious experiences allow one to build his or her beliefs through modelling influences by those similar to oneself. On the other hand, one's physiological states has been related to how one perceives one's personal capacity. For example, aches, fatigue and pain have been linked to physical inefficacy.[2]

Self-efficacy may be viewed as a double-edged sword as both its positive and negative effects have been reported. For instance, a meta-analysis based on 36 studies reported a positive and significant effect of self-efficacy on academic performance.[3] However, self-efficacy can sometimes lead to overconfidence. Moores and Chang[4] reported that a negative relationship was observed between self-efficacy and subsequent performance when overconfidence was taken into account. Besides, self-efficacy can also affect a person's thought patterns and behaviour. Low self-efficacy individuals tend to think that tasks are more difficult than they actually are, and thereby experience increased stress with poor task planning.[5]

Self-efficacy has been widely studied in the field of positive psychology. In one, study, self-efficacy of young adults significantly correlated to their life satisfaction (r=0.483,

p=0.000).[6] Although self-efficacy are not the same as self-esteem, they are closely related and are important aspects of the self-concept. Self-efficacy and self-worth have been viewed as two important factors of self-esteem and that they reinforce one another.[7] In one study investigating the relationship among loneliness, self-esteem and self-efficacy among college students, it was found that self-esteem was strongly correlated with self-efficacy (r =0.59, p <0.001). A negative and moderate correlation between loneliness and 1) self-esteem (r = -0.48, p <0.001) and 2) self-efficacy (r = -0.46, p <0 .001) was also observed in the same study.[8]

To this end, several studies have investigated the self-efficacy of medical students. However, these studies mainly relate to the students' self-efficacy to various learning activities such as problem-based learning, [9] knowledge and communication in adolescent medicine, [10] objective structured clinical examination (OSCE) performance.[11] Studies on the factors affecting medical students' self-efficacy are relatively few or lacking. There is also a scarcity of related research on optometry students, whereas a few sporadic studies reported the general self-efficacy of dental students.[12, 13]

Moreover, there are only a few comparative studies on the interdisciplinary differences in self-efficacy between medical and health sciences students in the published literature. [14, 15] Knowledge on the interdisciplinary differences in self-efficacy among medical and health sciences may be beneficial to the teachers and has practical significance as it is not uncommon that

the teachers often have to cross-teach various disciplines. Data generated from this study may help the teachers to adjust their teaching strategies based on these differences when dealing with students from different disciplines. This study, therefore, aimed to investigate the 1) interdisciplinary differences in the perceived general self-efficacy (GSE) among medical, dental and optometry students, 2) factors affecting their GSE, as well as 3) the effects of GSE on the students' academic performance.

Materials and Methods

Study design and sample size

This was a cross-sectional study carried out on preclinical (Year 1 and Year 2) medical and dental, as well as Year 1 and Year 2 optometry students at a Malaysian private university. A total of 231 students (86 medical, 81 dental and 64 optometry) took part in the study.

Study instrument

The General Self-efficacy Scale (GSES) [16] was used to determine the participant's perception of his or her ability to perform various tasks. The instrument has been validated in an earlier study.[17] The questionnaire has 10 items graded on 4-point Likert scale whereby 1 indicating 'definitely not true' and 4 indicating 'definitely true'. The GSE score ranges from 10 to 40, with a higher score indicating a higher self-efficacy. The participants were to provide information about their demographic data before attempting the questionnaire.

Permission and consent

Written permissions were obtained from the Deans of the Faculty of Medicine, Faculty of Dentistry and the Faculty of Optometry and Vision Sciences of the university in which the research was conducted. A written consent was obtained from voluntary participants from the three faculties before they attempted the questionnaires, which were anonymous and treated with confidentiality.

Statistical analysis

Analysis of data was carried out using the Statistical Package for the Social Sciences (SPSS) software version 22. Analysis of Variance (ANOVA) and t-test were used for comparisons of means. Relationship between two continuous variables was determined using Pearson's correlation. A p value of <0.05 was considered statistically significant.

RESULTS

Demographic data and response rate

The demographic data of the participants is summarised in Table 1. The overall response rate of the participant was 89.9%.

Table 1 Demographic data

Demographic data		Frequency
Age (year)	Min	17
	Max	25
	Mean	20.73
	SD	1.30
Gender (n, %)	Male	77 (33.3)
	Female	154 (66.7)
Race (n, %)	Malay	44 (19.0)
	Chinese	124 (53.7)
	Indian	25 (10.8)
	Other	38 (16.5)
Nationality (n, %)	Local	189 (81.8)
	International	42 (18.2)
Types of accommodation (n, %)	Staying with family	60 (26.0)
	On campus hostel	70 (30.3)
	Other	101 (43.7)
Household income (n, %)	Low income group	169 (73.2)
	High income group	55 (23.8)
	Unspecified	7 (3.0)
Academic achievements (n, %)	High achievers	103 (44.6)
	Non-high achievers	114 (49.4)
	Unspecified	14 (6.1)

Interdisciplinary differences in mean general self-efficacy scale (GSES) score among medical, dental and optometry students

The mean GSE scores of the students are summarised in Table 2. Overall, the mean GSE score for all students was 29.30 (*SD*=4.24). The medical students (*M*=31.28, *SD*=4.23) had the highest mean score. This was followed by the dental students (*M*=28.75, *SD*= 3.96) and the optometry students (*M*= 27.33, *SD*=3.45). Analysis of Variance (ANOVA) was statistically

significant [$F(2,228)=19.76$; $p=0.000$) when comparing the mean GSE scores of medical, dental and optometry students. The medical students scored significantly higher than the dental ($p=0.000$) and optometry students ($p=0.000$), whereas the dental students scored significantly higher than the optometry students ($p=0.000$) (Table 3).

Table 2 Mean GSES score of medical, dental and optometry students

Course	N	Mean	SD
Medical	86	31.28	4.23
Dental	81	28.75	3.96
Optometry	64	27.33	3.45
Overall	231	29.30	4.24

Table 3 Interdisciplinary differences in mean GSE scores

Discipline	Mean	SD	Discipline	Mean	SD	P value
Medical	31.28	4.23	Dental	28.75	3.96	0.000
Medical	31.28	4.23	Optometry	27.33	3.45	0.000
Dental	28.75	3.96	Optometry	27.33	3.45	0.000

Effects of demographic factors on self-efficacy

The demographic data of the students is summarised in Table 1 and the effects of various demographic factors on self-efficacy are summarised in Table 4. Age was observed to be weakly, positively and significantly correlated to the GSES score ($r=0.20$, $p=0.003$) whereas a significant gender difference was observed, with male students ($M=30.09$, $SD=4.54$) scoring significantly higher than female students ($M=28.90$, $SD=4.04$; $p=0.044$).

Nationality was also observed to play a role in the self-efficacy of the students, with the international students (*M*= 31.48, *SD*=4.48) demonstrated a higher mean GSES score than local students (*M*=28.81, *SD*=4.04), and the difference was statistically significant (*p*=0.001).

Table 4 Effects of demographic factors on self-efficacy

Age	**Correlation with GSE**			
	Pearson correlation	0.20		
	Significance (*p* value)	0.003		
		Mean	**SD**	**Significance (*p* value)**
Gender	Male	30.09	4.54	0.044
	Female	28.90	4.04	
Nationality	Local	28.81	4.04	0.001
	International	31.48	4.48	
Income	Lower income group	28.57	4.21	0.000
	Higher income group	31.47	3.74	
Accommodation	Staying with family	28.40	4.58	0.029
	Not staying with family/on campus	30.18	4.16	

The participants were divided into two income groups. Those in the higher income group had a monthly household

income >RM 5000 and those in the lower income group, <RM 5000. It was shown that those from the higher income group (*M*=31.47, *SD*=3.74) had a statistical significant higher mean GSES score than those from the lower income group (*M*=28.57, *SD*=4.21; *p*=0.000). ANOVA was significant (*F*(2,228)=4.12; *p*=0.017). When comparing the mean GSES scores among those who stayed with their families, those who stayed on campus and those whose accommodation were not staying with family or on campus, Post-hoc analysis showed that students who stayed with their families reported a statistical significant lower mean GSES score (*M*=28.40, *SD*= 4.58) than those students who were not staying with their families or on campus (*M*=30.18, *SD*= 4.16; *p*=0.029).

Effects of self-efficacy on academic achievements

The students were divided into two main groups according to their academic achievements. The high achievers refer to those who score the highest grades among their peers. It was shown that the high achievers had a higher mean GSES score (*M*=29.74, *SD*=4.12) than the non-high achievers (*M*=29.05, *SD*=4.32). However the difference was statistically not significant (*p*=0.234).

Table 5 Effects of self-efficacy on academic achievements

		Mean	**SD**	**Significance (*p* value)**
Academic achievements	High achievers	29.74	4.12	0.234
	Non-high achievers	29.05	4.32	

Discussion

Medical students in this study had a significant higher mean GSES score than the dental and optometry students, which contradicted the findings reported by Aboalshamat, Hou and Strodl,[14] in which there was no statistically significant difference in mean GSES scores between medical and dental students. However, interdisciplinary differences in the mean GSES score were observed in another study comparing medical, midwifery and nursing students, with the medical students scoring lower than midwifery students and higher than nursing students.[15] A probable explanation for the medical and dental students having a higher mean GSES score than that of the optometry students is that the medical and dental programs have higher entry requirements when compared to the optometry program. Hence, students of different self-efficacy levels might have been selected into the respectively programs. On the other hand, even though both the medical and dental programs have similar entry requirements, the nature of the programs are somewhat different. Hence, the difference in the mean GSES score between the medical and dental students may be due a difference in the characteristics and personalities of students that were being recruited into each program.

Age was found to play a role in the GSES score of medical and health sciences students in this study in which a weak, positive, and significant relationship existed between the two (r=0.20, p=0.003). This coincides with findings from a study conducted on student nurses, which reported a weak, positive and significant correlation between age and self-efficacy (r=0.233,

$p<0.01$).[18] Other than age, gender also played a role in the GSES scores of the students, with the male students scoring significantly higher than the female students. This finding is in tandem with previous studies as gender differences in self-efficacy have been commonly reported in the published literature with a male dominance in self-efficacy scores. [15, 19] It has been suggested that gender differences in self-efficacy may be due to the personality types of the students. This is because the relationship between gender and self-efficacy may not be a direct one as research has shown that gender-personality interactions play a role in gender differences in self-efficacy.[20]

Interestingly, international students demonstrated a significantly higher mean GSES score than the local students, whereas those who were not staying on campus or with their families scored higher than those staying with their families. There is a scarcity of research on the effects of nationality and accommodation on GSE of university students. Hence, it is difficult to compare findings of the current study with a previous study. One possible explanation for the observed findings is that the international students, as well as those not staying with their families or on campus are required to be more independent and self-reliant in their daily lives, which may, in turn, contribute a higher self-efficacy.

The family income of the students in this study also had a significant effect on the mean GSES scores. Those from the higher income group had a significantly higher mean score than those from the lower income group. This finding is in tandem with those from a study conducted on Chinese college students, in

which college students of low socioeconomic status scored significantly lower than their peers on general self-efficacy and subjective well-being.[21] However, another study by Çakar[6] reported no significant differences in self-efficacy and life satisfaction when comparing young adults from different levels of income (p>0.05). The influence of family income on self-efficacy may be explained by the fact that the expectations of others on the students from the higher income group and those from the lower income groups are different. This is because one's self-efficacy can be affected by the verbal persuasion of others concerning his or her competence[1].

Previous research has shown that self-efficacy is related to academic achievements,[3, 11, 19] with some studies reported a reciprocal relationship between the two. [22, 23] The finding from the present study, however, contradicts those from these studies. Although the high achievers scored higher in the mean GSES score when compared to the non-high achiever, the difference was statistically not significant. This is in tandem with findings of another study, which demonstrated a close to zero correlation between self-efficacy and observed communication skills rated by experts among medical students and young physicians. [24]

The findings generated from this study have practical implications. Knowing that there exist interdisciplinary differences in self-efficacy, the teachers who cross-teach the various disciplines can adjust their teaching strategies accordingly. Since age has been identified as a factor influencing the self-efficacy of the students, perhaps the teachers can also

adapt their teaching strategies for students in different years of study. Interventional measures such as giving frequent, focussed feedback, may be applied to the students with low self-efficacy.

Conclusions

This study concludes that 1) interdisciplinary differences existed among medical, dental and optometry students, 2) age, gender, nationality and the type of accommodation had an influence on the general self-efficacy of the students and 3) general self-efficacy had no significant effects on the students' academic achievements. As this study was limited to a small sample size and only Year 1 and Year 2 students, future research should include a bigger sample size. It should also include students from different levels of study from the beginning to the end of the course to determine if self-efficacy changes over time given the significant relationship with age observed in the present study.

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Original article

Inter -relationships between life satisfaction, self-esteem and perceived stress and their influence on academic achievements among medical and dental students at a Malaysian private university

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Abstract

Background: Life satisfaction, perceived stress and self-esteem have been found to be related to academic achievements of medical and dental students. However, the inter-relation of these three factors among medical and dental students has not been established.

Materials & Methods: This was a cross-sectional study carried out on 239 pre-clinical medical and dental students at a Malaysian private University using the Satisfaction with Life Scale (SWLS), Rosenberg Self-Esteem Scale (RSES) and the Perceived Stress Scale (PSS). Data was analysed using the Statistical Package for Social Sciences (SSPSS) version 22. The SWLS, RSES and PSS scores are expressed as mean ± standard deviation. Comparison of means was carried out using the independent t test. Correlation

of variables was carried out using Pearson's Correlation. A p value ≤ 0.05 is considered statistically significant and a p value of ≤ 0.001 is considered highly significant.

Results: Overall, medical and dental students showed an average level of life satisfaction (*M*=23.46, *SD*=5.52), moderate level of stress (*M*=20.49, *SD*=5.85) and normal self-esteem (*M*=17.61, *SD*=4.7). Among the three factors, only perceived stress had a significant effect on their academic achievements ($p<0.05$). All three factors also showed a significant correlation with one another ($p<0.05$).

Conclusions: Findings from this study suggest that stress management is important to medical and dental students as this helps with their academic performance and has an influence on their self-esteem, as well as life satisfaction.

Keywords: Life satisfaction; self-esteem; perceived stress; medical students; dental students

Introduction

Life of a medical or dental student is stressful due the heavy workload and the many challenges one has to endure throughout one's academic pursuit. Several studies have shown that medical students experience stress levels that are higher than the general population.[1-3] On the other hand, a study has demonstrated some considerable degree or severe stress among dental students.[4] While stress is not necessary a bad thing all the time, and may act as a motivating factor to some, chronic stress often has many negative and harmful effects on one's physical health.[5,6] Some

factors contributing to stress among medical students have been identified. These include environmental factors, new college environment, student abuse, tough study routines and personal factors.[7]

Not only can stress have an impact on one's physical health, it has also been shown to have an effect on one's mental health.[8, 9] Hence, it is not uncommon that medical and dental students experience depression. In a meta-analysis, it was reported that the global prevalence of depression among medical students was 28.0%.[10] On the other hand, burnout, depression and suicidal thoughts have also been reported among dental students.[11] Besides, the stress level of dental students has been shown to increase over the academic years with detrimental effects on both their health and academic performance[12] whereas stress has been negatively correlated to the academic performance of medical students.[13]

Life satisfaction refers to a positive cognitive evaluation of one's life, which is an important indicator of one's subjective well-being.[14] As life in medical and dental schools is very demanding and stressful - both mentally and physically, medical and dental students may be restricted from activities that are more life satisfying. As such several studies have been carried out to investigate the life satisfaction of medical and dental students in the past.[15,16] It is important to understand the life satisfaction of these students because a relationship between positive well-being and academic performance has been demonstrated among dental

students[17] whereas quality of life has been correlated to academic performance among medical students.[18]

Self-esteem may be defined as the positive or negative evaluations of oneself and how one feels about it.[19] According to Rosenberg, [20] self-esteem can be viewed as an attitude that raises one's sense of worthiness. It is important for medical and dental students to have appropriate views of themselves as self-awareness and self-directed learning are important elements of medical and dental education. Some factors that play a role in the self-esteem of a person include gender[21] and socioeconomic status.[22] Just like stress and life satisfaction, self-esteem has also been related to learning outcomes of students. In one study, those with a higher self-esteem were more successful in their academic achievements.[23] In another study, it has been demonstrated that self-esteem was a more significant contributor of academic performance among medical and health sciences students, when compared to stress or body image.[24] However, there have been contradictory views on the effects of self-esteem on academic performance. For example, Baumeister *et al* believe that a high self-esteem is the result rather than the cause of good academic performance.[25]

Although many studies have looked into the life satisfaction, perceived stress and self-esteem of medical students and dental students individually, there are not many studies that explore the inter-relationships between these three aspects in a single study. This study aimed to investigate the interplay between the life satisfaction, self-esteem and perceived stress of medical and

dental students at a private university in Malaysia. It also investigated their effects on the academic performance of these students.

Materials & Methods

This was a cross sectional study carried out at a private university in Malaysia to investigate the relationship between life satisfaction, self-esteem and perceived stress among medical and dental students.

Participants

The study was conducted on pre-clinical medical and dental students in a Malaysian private university. A total of 239 students (comprising of 104 Year 1 medical students, 44 Year 2 medical students, 49 Year 1 dental students and 42 Year 2 dental students) took part in the study.

Instruments

Three questionnaires were used in this study, namely, the Satisfaction with Life Scale (SWLS), the Rosenberg's Self-Esteem Scale (RSES) and the Perceived Stress Scale (PSS). All three instruments have been widely used in the published literature. Before attempting the questionnaires, the students filled in their demographic data and sign a consent form.

Satisfaction with Life Scale (SWLS)

The SWLS is commonly used to measure global life satisfaction. Life satisfaction is assessed by a 5-item Likert scale. Responses for all five items were on a 7-point scale, with 1 indicating

"strongly disagree" and 7 indicating "strongly agree". A higher overall score indicates a high level of life satisfaction.

Rosenberg's Self-Esteem Scale (RSES)

The RSES is a tool for assessing global self-esteem. It consists of 10 items. Items are anchored with a 4-point scale, ranging from 0 (strongly disagree) to 3 (strongly agree). However, 5 items are reversely scored (items 2,5,6,8 and 9). In general, the higher the score, the higher the self-esteem.

Perceived Stress Scale

The PSS questionnaire consists of 10 questions related to the participant's feelings and thoughts in the previous month. The participants were required to rate how often they felt or thought a certain way using a 5-point scale, where 0 indicates that they never experienced the condition mentioned in the question and 4 means that they experienced it often. The higher the overall score, the higher the level of perceived stress.

Consent and confidentiality

The students' participation in the study was voluntary. The participants signed a consent form prior to attempting the questionnaires, which were anonymous.

Statistical analysis

Data was analysed using the Statistical Package for Social Sciences (SSPSS) version 22. The SWLS, RSES and PSS scores are expressed as mean ± standard deviation. Comparison of means was carried out using either the independent t test.

Correlation of variables was carried out using Pearson's Correlation. A p value ≤ 0.05 is considered statistically significant and a p value of ≤ 0.001 is considered highly significant.

Results

Demographic data

The demographic data of the participants is summarised in Table 1.

Table 1 Demographic data of participants

Demographic factor		**Frequency**
Age (years)	Minimum	18
	Maximum	29
	Mean	20.95
	SD	1.27
BMI (kg/m^2)	Minimum	13
	Maximum	37
	Mean	21.97
	SD	4.11
Gender (n, %)	Male	85 (35.56%)
	Female	151 (63.18%)
	Unspecified	3 (1.26%)
Race (n, %)	Malay	85 (35.56%)
	Chinese	89 (37.24%)
	Indians	38 (15.90%)
	Others	22 (9.21%)
	Unspecified	3 (1.26%)
Family income (n, %)	Lower income group (< RM 10000)	144 (60.25%)
	Higher income group (>RM 10000)	75 (31.38%)
	Unspecified	20 (8.37%)
Academic achievement	High achievers	76 (29.29%)
	Non-high achievers	158 (66.12%)

	Unspecified	5(2.09%)

Mean SWLS, RSES and PSS scores among medical and dental students

The mean SWLS, RSES and PSS scores of medical and dental students are summarised in Table 2. A statistical significant difference in the mean RSES score was observed between the medical (*M*=18.13, *SD*=4.15) and dental students (*M*=16.78, *SD*=5.37; *p*=0.042). However, differences in mean SWLS and PSS scores between the medical and dental students were statistically not significant (p>0.05).

Table 2 Mean SWLS, RSES and PSS scores of medical and dental students

Course	**Score**	**Mean**	**SD**	**Significance (p value)**
Medical	SWLS	23.55	5.69	0.738
Dental		23.31	5.25	
Overall (medical & dental)		23.46	5.52	
Medical	RSES	18.13	4.15	0.042
Dental		16.78	5.37	
Overall (medical & dental)		17.61	4.70	
Medical	PSS	20.28	5.89	0.499
Dental		20.81	5.80	
Overall (medical & dental)		20.49	5.85	

Relationship between academic achievement and mean (i) SWLS, (ii) RSES and (iii) PSS scores

In this study, high achievers refer to the students who achieved the highest grades in the exams. There was a statistical significant difference in the mean PSS score in which the high achievers (*M*= 19.41, *SD*=5.89) scored significantly lower than the non-high achievers (*M*=21.07, *SD*=5.72; *p*=0.041). Differences in the mean SWLS and RSES scores were, on the other hand, statistically not significant (*p*>0.05) between the high achievers and non-high achievers. (Table 3).

Table 3 Relationship between academic achievements and mean (i) SWLS, (ii) RSES and (iii) PSS scores

	Achievement	Mean	SD	**Significance (p value)**
SWLS score	Non-high achiever	23.01	5.474	0.079
	High achiever	24.36	5.477	
RSES score	Non-high achiever	17.35	4.345	0.248
	High achiever	18.11	5.204	
PSS score	Non-high achiever	21.07	5.721	0.041
	High achiever	19.41	5.886	

Correlation between SWLS, RSES and PSS scores

The RSES score was moderately, positively, and significantly correlated with the SWLS score (*r*=0.49, *p*= 0.000) and was moderately, negatively and significantly correlated to the PSS score (*r*=-0.54, *p*=0.000). The SWLS score was moderately, negatively, and significantly correlated to the PSS score (*r*=-0.47, *p*=0.000) (Table 4).

Table 4 Correlation between SWLS, RSES and PSS scores

		RSES score	SWLS score	PSS score
RSES score	Pearson Correlation	1	0.490**	-0.536**
	Sig. (2-tailed)		0.000	0.000
SWLS score	Pearson Correlation	0.490**	1	-0.468**
	Sig. (2-tailed)	0.000		0.000
PSS score	Pearson Correlation	-0.536**	-0.468**	1
	Sig. (2-tailed)	0.000	0.000	

Discussion

In this study, medical students (*M*=23.55, *SD*=5.69) had a higher mean SWLS score than dental students (*M*=23.31, *SD*=5.25) but the difference was statistically not significant. A score between 20 and 24 implies that a person is generally satisfied with most areas of his or her life but would like some improvement in each area.[26] The findings suggest that both medical and dental students were in general satisfied with their life and these findings are in tandem with those from a previous study, which reported similar SWLS scores.[16]

Overall, the mean RSES scores of medical and dental students were in the range of normal (i.e. between 15 and 25). Medical students (*M*=18.13, *SD*= 4.15) also had a higher mean RSES score when compared to that of dental students (*M*=16.78, *SD*= 5.37), and the difference was statistically significant (*p*=0.042). Although literature comparing the RSES scores of medical and dental students is scarce, a significant

interdisciplinary difference in the RSES score has been reported in one study comparing medical, midwifery and nursing.[27]

Medical (*M*=20.28, *SD*= 5.89) and dental students (*M*= 20.81, *SD*= 5.80) in this study reported a moderate level of stress (i.e. between 14 and 26), which was comparable with finding in a study carried out on medical students in India (*M*=24.91, *SD* 7.31),[28] and lower than that in a study carried out on Pakistani medical students (*M*=30.84, *SD* = 7.01). [29] However, this may be due to the different settings of the medical schools in these studies. The difference in the mean PSS score was statically not significant between medical and dental students.

Life satisfaction of medical and dental students did not have a significant effect on academic achievement. Although the high achievers had a higher mean SWLS score, there was no statistical significant difference in the score between the high achievers (*M*=23.01, *SD*=5.47) and non-high achievers (*M*=24.36, *SD*=5.48). This finding contradicts that in a study conducted on dental students in which academic performance was related to the positive well-being, [17] and that in a study on medical students, which showed a relationship between academic performance and quality of life.[18] Other studies have also reported a significant relationship between academic achievement and life satisfaction. For example adolescent students' GPA has been shown to significantly correlate to life satisfaction ($p<0.01$)[30] and a positive reciprocal causal relations between students' life satisfaction and grades has been reported in another study.[31]

In addition, although the mean RSES score of the high achievers (*M*=18.11, *SD*=5.20) was higher than that of the non-high achievers (*M*=17.35, *SD*=4.35), the difference was statistically not significant (p>0.05) which contradicted the findings of several other studies in which students with high self-esteem had better academic performance.[23, 24] However, it is not sure whether good academic achievements is the cause or the result of a high self-esteem. Some researchers believe that good performances lead to a high self-esteem but not the other way round. Bowles specifically measured the self-esteem of students right after they obtained their exam grades and the positive correlation between the two was consistent with the view that self-esteem is a result, rather than the cause of doing well in school.[32] On the other hand, other researchers "have not found evidence that boosting self-esteem (by therapeutic interventions or school programs) causes benefits" and their findings "do not support continued widespread efforts to boost self-esteem in the hope that it will by itself foster improved outcomes."[25]

Interestingly, the perceived stress of the students was the only factor that had a statistical significant relationship with their academic achievements. The high achievers (*M*=19.41, *SD*=5.89) significantly perceived a lower level of stress when compared with the non-high achievers (*M*=21.07, *SD*=5.721; *p*=0.041). This finding is in tandem with those from other studies in which a negative relationship between stress and academic performance has been reported. [12, 13, 33]

The relationship between life satisfaction, self-esteem and perceived stress is interesting in this study in that all three factors were found to be inter-related to each other. The SWLS score demonstrated a moderate, positive and significant correlation with the RSES score (r=0.49, p= 0.000) but a moderate, negative and significant correlation with the PSS scores(r=-0.47, p=0.000). On the other hand, the PSS score was moderately, negatively and significantly correlated to the RSES score(r=-0.54, p=0.000).

A significant positive relationship between life satisfaction and self-esteem in the present study coincides with findings in previous studies.[34, 35] This is because self-esteem is an important predictor of happiness, and that a high self-esteem predicts lower levels of depression.[36] Results of previous studies, as well as the current study are in agreement with earlier research by Diener and Diener, in which self-esteem was found to be a strong predictor of life satisfaction.[37]

The relationship between life satisfaction and stress was negative and significant in this study. This is consistent with the findings from previous studies[38-40] which suggest that perceived stress is a useful predictor of life satisfaction. However, Matheny, Roque-Tovar and Curlette reported that the use of perceived stress together with coping resources give a more accurate prediction of life satisfaction.[41]

The negative relationship between stress and self-esteem also coincides with findings from previous studies.[42, 43] However,

the causal relationship between the two is complex. Perception appears to be the point of interaction between self-esteem and stress. Generally, a low self-esteem makes a person vulnerable to stressful situations. On the other hand, a high self-esteem is protective against stressful events as those who have a high self-esteem generally have a positive approach in their perception of things.[44] However, increasing levels of stress may be detrimental to one's self-esteem especially with time.[45]

The present study has established the effects of (i) life satisfaction, (ii) self-esteem and (iii) perceived stress on the academic achievements and the inter-relation between these three factors among medical and dental students at a Malaysian private university. However, there were some limitations in this study which include a small sample size limited to only first and second year medical and dental students, and that the study was a cross-sectional study that explored the three factors at a single point of time.

Conclusions

Several points can be concluded from this study. Firstly, medical, and dental students who took part in the study were in general having (i) an average level of satisfaction with their lives, (ii) a self-esteem within normal range and (iii) a moderate level of perceived stress. Secondly, among the three factors, only perceived stress had a significant effect on their academic achievements. Last but not least, significant correlation existed between (i) life satisfaction and stress, (ii) stress and self-esteem

and (iii) life satisfaction and self-esteem, suggesting that these three factors are inter-related among medical and dental students.

This implies that stress management plays an important role among these students as it may help improve their academic achievements. Given the relationship with life satisfaction and self-esteem, a less stressed student may also have an improved life satisfaction and a higher self-esteem. Therefore, it may be beneficial if medical and dental schools help their students to develop coping strategies to combat stress throughout their academic pursuit. Based on the current study, it is recommended that future studies should include (i) a bigger sample size, (ii) students from different levels of study, and (iii) exploration of the effectiveness of various coping strategies with regards to academic achievements.

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Original article

Formulation and Evaluation of Topical Acyclovir Gel Using Different Polymers

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Abstract

Background: Acyclovir is usually given as protracted therapy and at greater dosing frequency for complete remittance of the disease due to its low oral bioavailability, but this is associated with side effects. Topical preparations of acyclovir are the alternative route of administration to treat local dermatological diseases caused by herpes simplex virus.

Objective: To prepare and evaluate the topical gel formulations of acyclovir by using different polymers.

Materials and Methods: Acyclovir gels were formulated by using three types of polymers, namely carboxymethylcellulose sodium (CMC Na), hydroxypropyl methylcellulose (HPMC) and carbopol-940 as gelling agents at different concentrations. They were evaluated for several physicochemical characteristics including physical appearance, grittiness, viscosity, spreadability, pH, drug content uniformity and *in vitro* drug release studies. The *in vitro* drug release of acyclovir from the selected gel formulations was evaluated as per the procedure described in United States Pharmacopoeia (USP), by using the standard 40

mesh stainless steel dissolution basket (USP Apparatus 1) containing cellulose acetate membrane with phosphate buffer pH 6.8 as the dissolution medium.

Results: Among all prepared gel formulations, formulation F8 containing 3% *w/w* of carboxymethylcellulose sodium was selected as optimal gelling agent in acyclovir gel formulation due to its desired physicochemical characteristics and it showed the highest acyclovir *in vitro* release rate of 96.21 ± 0.92% over 5 hours.

Conclusion: The release of acyclovir from the gel formulations was significantly affected by the type and concentration of polymer (*p*-value < 0.05).

Keywords: Acyclovir, carbopol-940, carboxymethylcellulose sodium, hydroxypropyl methylcellulose, *in vitro* drug release studies.

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Introduction

Acyclovir is an antiviral medicine primarily used to treat herpes simplex virus (HSV) infections, varicella-zoster and herpes zoster.[1-2] Acyclovir has relatively low oral bioavailability (15% to 30%) mainly due to poor water solubility and its absorption is variable, slow and incomplete.[3] Therefore, acyclovir

is usually given as protracted therapy and at greater dosing frequency for complete remittance of the disease. However, this may lead to unintended side effects for some people.

Topical preparations of acyclovir are the alternative route of administration for overcoming the challenge of poor bioavailability to treat dermatologic manifestations of herpes simplex. Drug delivery across the skin enables drugs to be targeted locally to the desired delivery area, hence, potential systemic side effects can be significantly reduced. Furthermore, it avoids metabolic degradation, gastrointestinal irritation, first-pass metabolism and frequent dosing associated with oral therapy of acyclovir.[4,5] Several semisolid preparations are used for topical drug deliver across the skin, and one of this is "gel".

The essential part of a gelling system is made up of a variety of polymers. Gel formulations show variation with the variability of polymer type and concentration which affect drug release and hence the formula quality which must be optimised. Among the many reasons for this study to be conducted is that there is no similar research study done for acyclovir gel formulation by using different types of polymers at different concentrations. Therefore, the main objectives of this research study include:

1. To formulate topical acyclovir gel formulations by using three types of polymers as gelling agents with different concentrations, namely carboxymethylcellulose sodium (CMC Na), hydroxypropyl methylcellulose (HPMC) and carbopol-940.

2. To evaluate the physicochemical characteristics of the formulated gels.
3. To study the effect of polymer type and concentration on the *in vitro* release rate of acyclovir from the prepared gel formulations.

Materials and Methods

Materials

Acyclovir (gift sample from Hovid research laboratory), carbopol-940, hydroxypropyl methylcellulose, M.N. 86,000, viscosity 4,000 cPs (2% solution), carboxymethylcellulose sodium (medium viscosity), 1,2 - propylene glycol, methylparaben, triethanolamine, sodium hydroxide and potassium dihydrogen phosphate.

Methods

Preparation of gels

In semisolid dosage form, gelling agents are used at a concentration of 0.5% to 10%, depending on the agent.[6] In this study, acyclovir gels were prepared by using three different polymers, namely CMC Na, HPMC and carbopol-940 at different concentrations of each polymer (1%, 3% and 5% *w/w*). The concentration of acyclovir in all the formulations remained constant (1% *w/w*). The composition of different formulations is listed in Table 1.

Table 1: Composition of acyclovir topical gel formulations (% *w/w*).

Ingredients	Formulation code								
	F1 (g)	F2 (g)	F3 (g)	F4 (g)	F5 (g)	F6 (g)	F7 (g)	F8 (g)	F9 (g)
Acyclovir	1	1	1	1	1	1	1	1	1
Carbopol-940	1	3	5	-	-	-	-	-	-
HPMC	-	-	-	1	3	5	-	-	-
CMC Na	-	-	-	-	-	-	1	3	5
Propylene glycol	20	20	20	20	20	20	20	20	20
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Triethanolamine	1.0	1.0	1.0	-	-	-	-	-	-
Distilled water q.s.	100	100	100	100	100	100	100	100	100

The gel bases were prepared by dispersing the required amount of the polymers in 10 g of propylene glycol (PG) and 50 g of distilled water with constant stirring by using a spatula at 75°C. Adequate amount of triethanolamine was added to adjust the pH of carbopol-940 gels. Then, the gel bases were left overnight at room temperature (25 ± 2°C) to gain complete hydration and swelling of the polymers.

On the other hand, accurately weighed 1 g of acyclovir powder and 0.1 g of methylparaben were dissolved in 10 g of PG and the remaining amount of distilled water to make up the final volume with constant stirring by using a magnetic stirrer (350 rpm for 30 minutes at 75°C). Next, the solvent blends were transferred slowly to the previously formed CMC Na, HPMC and carbopol-940 gel bases. Lastly, the mixtures were continuously stirred

gently with a spatula for an additional 30 minutes to obtain homogenous gels.

Evaluation of prepared gel formulations

Physical appearance: The prepared gels were observed visually from the container for colour, homogeneity, transparency, and consistency.[6]

Grittiness: The prepared gels were assessed microscopically for the absence of particles.[6]

pH measurements: Eutech CyberScan pH 510 meter was used to measure the pH of the prepared gels.[7] The pH meter was calibrated with standard buffer solutions at a pH of 4.00, 7.00 and 10.00 before starting pH measurement. After calibration, the electrode of the pH meter was immersed into the sample 2 minutes prior to taking the pH reading at room temperature. Measurements were conducted in triplicate for each prepared gel formulation.

Viscosity studies: The viscosity of the prepared gels was measured by using a Brookfield viscometer at room temperature.[7] Spindle number 07 was selected, and it was lowered perpendicularly into the gel. Later, the spindle was rotated at 10 rpm until the readings were stabilised and the corresponding dial reading was recorded in centipoises (cPs).

Spreadability: The spreadability of the prepared gels was measured by spreading 1 g of each gel formulation on a 2 cm original diameter circle pre-marked on a glass plate. This glass plate was covered with a second glass plate of the same

dimension. Later, an object weighs 1000 g was placed on top of the two slides for 1 minute and the diameter of the circle was measured (in cm) after spreading of the gel.[8,9] Measurements were conducted in triplicate for each prepared gel formulation. Spreadability was calculated by using the following formula:

Spreadability = X_1 cm – 2 cm. where, X_1 = the spreading diameter

Drug content uniformity

One gram of accurately weighed gel formulation (equivalent to 10 mg of acyclovir) was dissolved in 100 mL of phosphate buffer pH 6.8 with constant stirring by using a magnetic stirrer at 350 rpm for 1 hour to get complete solubility of the drug. From that 10 mL of solution was taken and diluted to 100 mL with the same buffer solution. After that, the absorbance readings were measured by using Beckman Coulter DU®730 Ultraviolet-Visible (UV-Vis) spectrophotometer at 250 nm. Then, the amount of acyclovir (µg/mL) was determined from the standard calibration curve.[7] Measurements were conducted in sextuplicate for each prepared gel formulation. The percentage of drug content in different formulations was calculated by using the following formula:

$$\text{Percentage of Drug Content} = \frac{\text{Concentration (µg/mL) x Final Volume x Dilution Factor / 1000}}{\text{10 mg}} \text{ X } 100\%$$

where, Final Volume = 100 mL, Dilution Factor = $\frac{\text{100 mL}}{\text{10 mL}} = 10$

In vitro drug release

The *in vitro* release of acyclovir from the selected gel formulations was evaluated as per the procedure described in United States Pharmacopoeia (USP), by using the standard 40 mesh stainless steel dissolution basket (USP Apparatus 1).[10] Phosphate buffer pH 6.8 was used as the dissolution medium throughout the test. The basket screen was covered with cellulose acetate membrane. The membrane was soaked overnight in the dissolution medium prior to use. The bath temperature was kept constant at 32 ± 0.5°C throughout the test to reflect normal skin temperature. Accurately weighed 5 g of each selected gel formulations (equivalent to 50 mg of acyclovir) were filled into the reservoir of the basket apparatus. The appropriate amount of the dissolution medium (900 mL) was added to the dissolution vessel and the shafts were rotated at 200 rpm to start the test. Aliquots of 10 mL were withdrawn at time intervals of 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes. They were replaced immediately by same amount of fresh dissolution medium to maintain constant volume. After that, the amount of acyclovir in the samples was analysed by measuring the absorbance readings using Beckman Coulter DU®730 UV-Vis spectrophotometer at 250 nm and the cumulative percentage drug release of each selected formulation was calculated.

Analytical method validation

Determination of the wavelength of maximum absorbance

Accurately weighed 0.1 g acyclovir powder was dissolved in adequate amount of phosphate buffer pH 6.8 and the volume was

finally made up to 100 mL with the same buffer solution in a volumetric flask to get a standard stock solution (1 mg/mL). After that, 1 mL of standard stock solution was withdrawn and diluted to 100 mL with the same buffer solution in another volumetric flask to obtain a working standard solution (10 µg/mL). Later, the working standard solution was scanned from 200 to 700 nm on a Beckman Coulter DU®730 UV-Vis spectrophotometer.[11]

Robustness

The robustness of the proposed UV-Vis spectrophotometric method was tested by analysing the acyclovir working standard solution under different wavelength conditions (250 nm ± 1). The absorbance readings were determined in sextuplicate for each wavelength condition and the results were represented as relative standard deviation (RSD).

Linearity and range

The establishment of linearity requires a minimum of five concentrations of the target analyte.[12] One millilitre of prepared standard stock solution was withdrawn and the volume was finally made up to 100 mL with phosphate buffer pH 6.8 in a volumetric flask to get a concentration of 10 µg/mL and serial dilutions for linearity were prepared to obtain required concentrations of 5, 2.5, 1.25 and 0.625 µg/mL. Next, the absorbance of the diluted sample solutions was determined in triplicate at 250 nm by using Beckman Coulter DU®730 UV-Vis spectrophotometer at a concentration range of 0.625-10 µg/mL.

A calibration curve of absorbance versus concentration (µg/mL) was plotted.

Specificity

The specificity of the proposed UV-Vis spectrophotometric method was evaluated by comparing the ultraviolet (UV) spectra of blank gels (placebo) against the acyclovir working standard solution. Moreover, the selected acyclovir gel formulations (sample) were scanned from 200 to 700 nm on a Beckman Coulter DU®730 UV-Vis spectrophotometer and checked for any changes in the UV spectra.

Accuracy

The accuracy of the proposed UV-Vis spectrophotometric method was evaluated with the help of the percentage of recovery, SD and RSD by using recovery experiments.[12] Samples were prepared at three levels 80%, 100% and 120% of the test concentration (10 µg/mL*)* by using the prepared standard stock solution. Next, the absorbance of each level was taken in triplicate by using Beckman Coulter DU®730 UV-Vis spectrophotometer at 250 nm.[13]

Precision

The precision of the analytical method was demonstrated by intra-day precision (repeatability) and inter-day precision (intermediate precision).[12] The intra-day precision was tested by performing the *in vitro* drug release studies on six determinations of the similar formulation in the same day, whereas the inter-day precision was

evaluated by performing the *in vitro* drug release studies on six determinations of the similar formulation per day for three consecutive days.[12] The mean, SD and RSD for each of the selected formulations were calculated from the observed absorbance readings by using the final time point of the *in vitro* drug release studies at 300 minutes.

Statistical analysis

One-way Analysis of Variance (ANOVA) was used to perform statistical comparisons by using IBM SPSS Statistic version 21.0 software at a significance level of p-value < 0.05.

Results

Evaluation of prepared gel formulations

Physical appearance

Table 2: Physicochemical characteristics of the formulated gels.

Formulation Code	Homogeneity	Colour	Consistency	Transparency	Grittiness	pH	Viscosity (cPs)	Spreadability (cm)	Drug Content (%)
F1	+++	White	Semi solid	Translucent	No	6.31 ± 0.02	21850	3.93 ± 0.06	99.1 ± 0.24
F2	+++	White	Semi solid	Translucent	No	5.22 ± 0.01	32950	3.60 ± 0.10	97.7 ± 0.23

F3	++	White	Semi solid	Translucent	No	4.63 ± 0.03	34200	2.83 ± 0.15	93.1 ± 0.22
F4	+++	White	Semi fluid	Transparent	No	5.11 ± 0.02	200	7.13 ± 0.21	95.1 ± 0.24
F5	+++	White	Semi solid	Translucent	No	5.04 ± 0.02	2450	5.63 ± 0.15	93.8 ± 0.44
F6	++	White	Semi solid	Translucent	No	5.02 ± 0.02	45300	3.97 ± 0.15	90.7 ± 0.46
F7	+++	White	Semi fluid	Transparent	No	6.14 ± 0.02	350	7.83 ± 0.15	93.5 ± 0.31
F8	+++	White	Semi solid	Translucent	No	5.98 ± 0.02	5050	5.27 ± 0.12	96.0 ± 0.42
F9	++	White	Semi solid	Translucent	No	6.38 ± 0.01	30750	3.43 ± 0.15	91.7 ± 0.21

Notes:

Excellent +++; Good ++; Poor +

Semisolid = More viscous; Semifluid = Less viscous

***In vitro* drug release studies (Table 3)**

Table 3: Cumulative percentage drug release of formulations F2, F5, F8 and F9 at different time intervals.

Time (minutes)	***Cumulative Drug Release (%)**			
	Carbopol-940 3% gel (Formulation F2)	HPMC 3% gel (Formulation F5)	CMC Na 3% gel (Formulation F8)	CMC Na 5% gel (Formulation F9)

0	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
30	15.29 ± 0.43	18.55 ± 0.13	23.28 ± 0.31	9.64 ± 1.48
60	21.60 ± 1.46	29.02 ± 1.62	35.78 ± 4.26	16.29 ± 2.05
90	27.89 ± 3.48	40.38 ± 2.29	45.93 ± 4.42	23.39 ± 2.01
120	34.85 ± 6.72	48.00 ± 0.71	57.15 ± 8.24	30.71 ± 3.45
150	41.86 ± 4.78	54.11 ± 0.21	64.24 ± 7.80	36.14 ± 3.38
180	48.63 ± 3.73	60.93 ± 0.58	74.03 ± 6.45	40.51 ± 2.56
210	55.29 ± 2.37	69.64 ± 0.88	81.88 ± 6.38	44.68 ± 2.87
240	61.29 ± 1.96	77.42 ± 0.61	89.37 ± 5.78	48.40 ± 2.53
270	67.48 ± 1.90	85.86 ± 2.06	95.21 ± 0.90	52.82 ± 3.00
300	72.61 ± 2.39	93.57 ± 0.77	96.21 ± 0.92	57.00 ± 3.07

*The results were expressed as mean ± SD; n=18.

Analytical method validation (Table 4-5)

Table 4: Results of robustness studies at three different wavelengths.

	Wavelength (nm)		
	249	250	251
*Mean absorbance ± SD	0.554 ± 0.001	0.558 ± 0.001	0.559 ± 0.001
RSD (%)	0.18	0.18	0.18

*n=6; RSD = relative standard deviation.

Table 5: Results of accuracy studies.

Recovery Level	Concentration (µg/mL)	Concentration Found	% Recovery	Mean % Recovery	SD	RSD (%)
80%	8	7.914	98.93	99.27	0.310	0.31
	8	7.946	99.33			
	8	7.963	99.54			
100%	10	9.933	99.33	99.33	0.325	0.33
	10	9.966	99.66			
	10	9.901	99.01			
120%	12	11.936	99.47	99.43	0.476	0.48
	12	11.985	99.88			
	12	11.871	98.93			

Precision (Table 6-7)

Table 6: Results of intra-day precision studies.

Formulation Code	*Mean absorbance	SD	RSD (%)
F2	2.238	0.043	1.92
F5	2.989	0.056	1.87
F8	3.078	0.000	0.00
F9	1.892	0.035	1.85

*n=6.

Table 7: Results of inter-day precision studies.

Formulation Code	*RSD (%)			Mean RSD (%)
	Day 1	Day 2	Day 3	
F2	1.92	2.06	1.99	1.99
F5	1.87	1.95	2.01	1.94
F8	0.00	0.00	0.00	0.00
F9	2.04	1.99	1.85	1.96

*n=6 (six determinations per day for three consecutive days).

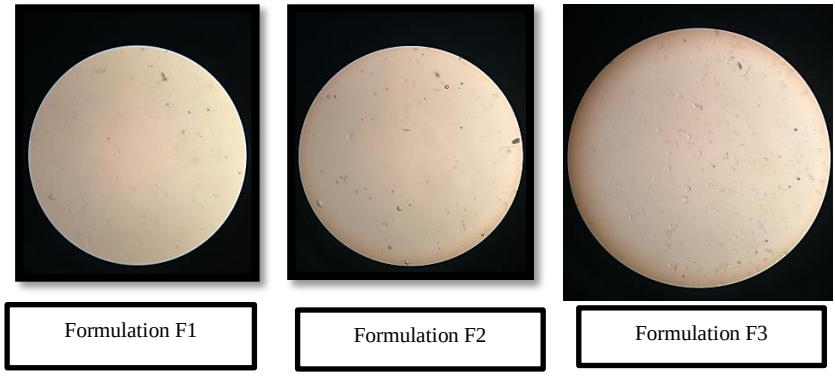


Figure 1: Light microscopy images of acyclovir gels (40x magnification) formulated by using carbopol-940 at (a) 1% *w/w*, (b) 3% *w/w* and (c) 5% *w/w*.

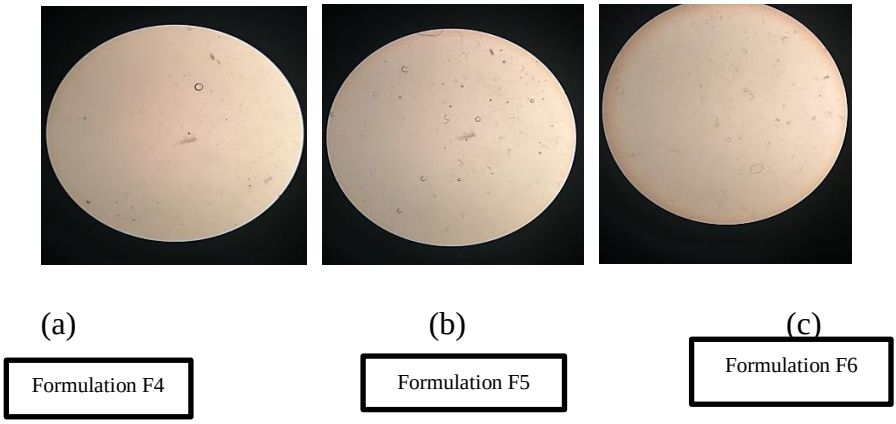
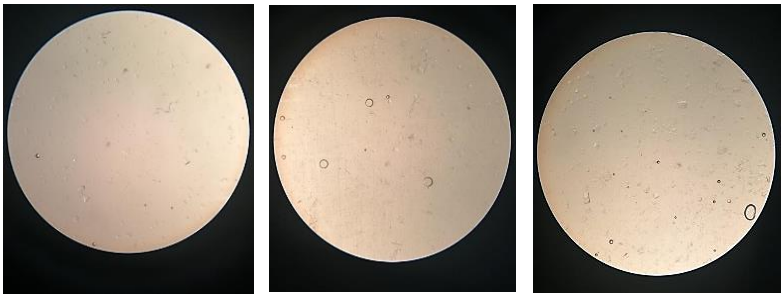


Figure 2: Light microscopy images of acyclovir gels (40x magnification) formulated by using HPMC at (a) 1% *w/w*, (b) 3% *w/w* and (c) 5% *w/w*.



(a) (b) (c)

Formulation F7 Formulation F8 Formulation F9

Figure 3: Light microscopy images of acyclovir gels (40x magnification) formulated by using CMC Na

Discussions

Evaluation of prepared gel formulations

Physical appearance

a) **Homogeneity (Table 2):** All formulated gels were evaluated for the existence of any aggregates and their appearance. Formulations F1, F2, F4, F5, F7 and F8 were smooth and showed excellent homogeneity with the absence of lumps, whereas formulations F3, F6 and F9 were stiff and showed good homogeneity with little presence of lumps. This can be attributed to the concentration of polymer was highest in formulations F3, F6 and F9 at 5% *w/w* when compared to other formulations.
b) **Colour (Table 2):** All formulated gels were white in colour.
c) **Consistency (Table 2):** All formulated gels were semisolid dosage form except formulations F4 and F7 which were semifluid dosage form. This can be attributed to the

concentration of HPMC and CMC Na were lowest in formulations F4 and F7 respectively at 1% *w/w* when compared to other formulations. The factor was not being applied to formulation F1 containing 1% *w/w* of carbopol-940 because this type of polymer showed high viscosity at low concentrations, therefore it can easily form semisolid gels at low concentrations.[14]

d) **Transparency (Table):** All formulated gels were translucent except formulations F4 and F7 which were transparent. This can be attributed to both formulations F4 and F7 had the lowest concentration of polymer at 1% *w/w*, were shown as semifluid.

Grittiness (Table 2): All formulated gels showed no grittiness under a light microscope (40x magnification). Therefore, all formulated gels fulfilled the requirements of the absence of grittiness and particulate matter as anticipated for any topical formulation.[15]

pH measurements (Table 2): The pH values of all formulated gels ranged from 5.02 ± 0.02 to 6.38 ± 0.01. Since topical preparations will be directly applied onto the skin, their pH should be compatible with the skin pH. The skin should be weakly acidic ranged from pH 4.0 to 7.0 depending on location.[16] The results showed that the pH of all formulated gels was found to be within the normal pH range of the skin, which was considered acceptable to avoid the risk of skin irritation at the application site. Therefore, the results indicated that the acceptability of these formulated gels for topical use.

Viscosity studies (Table 2): The viscosity of various formulated acyclovir gels was found in the range of 200 to 45300 cPs. There was a nearly twofold increase in the viscosity from 1% *w/w* to 5% *w/w* of carbopol-940 concentration. The increase of HPMC concentration from 1% *w/w* to 5% *w/w* increased viscosity almost 227 times while the viscosity increased nearly 88 times from 1% *w/w* to 5% *w/w* of CMC Na concentration. Therefore, it was clear that the viscosity increased as the concentration of polymer in the gel formulations increased (p-value < 0.05).

Spreadability (Table 2): The larger is the spreading diameter, the more spreadable is the sample, and vice versa. The spreadability of all formulated gels ranged from 2.83 ± 0.153 cm to 7.83 ± 0.153 cm. However, there are no established guidelines on the ideal spreadability value. Therefore, it could be said that all the gels were easily spreadable. The spreadability of the gel formulations increased with decreasing polymer concentration. Statistical analysis using one-way ANOVA showed that the spreadability of the gel formulations was significantly affected by the polymer concentration (p-value < 0.05). Furthermore, it was particularly noteworthy that the spreadability of a gel had been shown to be related to its rheological characteristics. In brief, the viscosity of the gel formulations was increased as the polymer concentration increased. Meanwhile, the spreadability of the gel formulations was decreased.

Drug content uniformity (Table 2): All formulated gels were observed to contain 90.7 ± 0.460% to 99.1 ± 0.239% of acyclovir, which were lying within the pharmacopeial limits (90.0% to

110.0%) as stated in the USP.[17] The results showed that acyclovir was distributed evenly throughout the gel in all formulations. Therefore, the method employed to prepare gel formulations in this study was found suitable.[18]

In vitro drug release studies (Table 3)

Formulations F2, F5 and F8 were selected for further *in vitro* drug release studies due to their acceptable physicochemical characteristics to examine the effect of different polymer types on the release of acyclovir from the prepared gel formulations at the same polymer concentration (3% *w/w)*. The results showed that cumulative percentage drug release was highest for formulation F8, followed by formulation F5 and formulation F2 with the value of 96.21 ± 0.92%, 93.57 ± 0.77% and 72.61 ± 2.39% respectively at the end of 5 hours (Table 3 and Figure 1). One-way ANOVA analysis showed that the release of acyclovir from the prepared gel formulations was significantly affected by the type of polymer (p-value < 0.05). From this study, it was found out that the acyclovir gel formulated by using CMC Na showed maximum drug release rate over 5 hours.

Formulation F8 (3% *w/w* CMC Na) was selected as optimised formulation due to better cumulative drug release over 5 hours compared to formulations F2 and F5. Therefore, formulation F9 (5% *w/w* CMC Na) was further studied for *in vitro* drug release to investigate the effect of the concentration of polymer on the release of acyclovir from the prepared gel formulations. The results showed that the cumulative percentage drug release was 96.21 ± 0.92% for formulation F8 and 57.00 ±

3.07% for formulation F9 at the end of 5 hours (Table 1 and Figure 2). It was found that the release of acyclovir from the prepared gel formulations increased as the concentration of CMC Na decreased from 5% to 3%. One-way ANOVA analysis showed that the release of acyclovir from the prepared gel formulations was significantly affected by the concentration of polymer (p-value < 0.05).

It was clear from the above analysis that the drug release increased with decreasing polymer concentration. On the other hand, viscosity decreased as the concentration of polymer decreased. Therefore, the viscosity was inversely proportional to the release of acyclovir from the prepared gel formulations.[19] Formulation F9 showed lower drug release as compared to formulation F8 attributed to its higher concentration of polymer. The higher the polymer concentration in a gel formulation, the more rigid the three-dimensional network structure of the gel system, and the greater its viscosity, hence, the lower the drug release rate.[19] This may be due to the drug was entrapped in the smaller polymer molecules at the higher polymer concentration, causing a greater resistance to the diffusion of drug molecules through the gel matrix, thus decreased drug release rate.[19] Besides, the tortuosity of the gel matrix increased with increasing polymer concentration may be another possible cause for decreased drug release rate since the drug molecules have to travel a longer pathway to diffuse through the gel matrix.[14]

Analytical method validation (Table 4-5)

Determination of the wavelength of maximum absorbance

The UV scan of the working standard solution between 200 to 700 nm displayed the absorption maximum (λ max) at 250 nm for acyclovir. Therefore, the same λ max was used as the working wavelength for further measurements of the drug.

Robustness

The typical RSD for UV analysis is usually not more than 2%.[20] The results of the robustness test were within the acceptable range as shown in Table 4, indicated that the absorbance remained unaffected by small variation. Therefore, the proposed UV-Vis spectrophotometric method was considered as robust.

Linearity and range

Linearity was evaluated by using the least square regression method. The acceptance criteria for the coefficient of determination (R^2) should be ≥ 0.98.[20] As shown in Figure 3, The linear regression equation was obtained as $y = 0.0614x - 0.0139$ and the R^2 for the calibration curve was found to be 0.9996. Therefore, the high R^2 value ($R^2 \geq 0.98$) indicated clear correlations between the acyclovir concentrations and their absorbance within the test ranges.

Specificity

The UV spectra of the placebo showed no peak at the specific wavelength of acyclovir. However, the absorption peak of the selected acyclovir gel formulations at 250 nm was unchanged in the presence of the other excipients in the sample, indicated no effects of the excipients on the UV absorption of acyclovir. Therefore, it can be said that the proposed UV-Vis

spectrophotometric method was specific for the determination of acyclovir in topical gel formulations.

Accuracy

The acceptance criteria for the percent recovery should be 98% to 102% and the RSD is ≤ 2%.[12] The results showed that the mean percent recoveries for lower (8 µg/mL), intermediate (10 µg/mL) and higher (12 µg/mL) concentrations were found to be 99.27%, 99.33% and 99.43% respectively as shown in Table 5. Therefore, the proposed UV-Vis spectrophotometric method showed good accuracy because the results were within the limits with their low RSD values (RSD < 1%).

Precision (Table 6-7)

The acceptance criteria for both inter-day and intra-day precision tests should have a statistical RSD ≤ 2%.[12] The results showed that the RSD values of the four selected formulations were observed to be within the acceptable range for both of these tests as shown in Table 6 and Table 7. Therefore, the proposed UV-Vis spectrophotometric method was precise, reproducible and repeatable.

Conclusion

In the present study, acyclovir gels were successfully formulated by using three types of polymers as gelling agents with different concentrations, namely CMC Na, HPMC and carbopol-940. Viscosity studies showed that the viscosity of the gel formulations increased as the polymer concentration increased. Spreadability studies showed that the spreadability of

the gel formulations was significantly affected by the polymer concentration (p-value < 0.05). Moreover, the spreadability of the gel formulations decreased with increasing the polymer concentration. In short, the viscosity of the gel formulations increased as the polymer concentration increased. Meanwhile, the spreadability of the gel formulations was decreased. Furthermore, the *in vitro* drug release studies showed that the release of acyclovir from the prepared gel formulations was significantly affected by the type and concentration of polymer (p-value < 0.05). Among all prepared gel formulations, formulation F8 containing 3% *w/w* of CMC Na was selected as optimal gelling agent in acyclovir gel formulation due to its desired physicochemical properties and it showed the highest acyclovir *in vitro* release rate of 96.21 ± 0.92% over 5 hours. Therefore, it can be concluded that the topical acyclovir gels formulated in this study could be an alternative option for the effective management of HSV skin infections.

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