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Development And Characterisation (Drug Loading, Drug Release And Expansion Study) Of Carboxymethylcellulose – Sodium Alginate Based Hydrogel As Wound Dressing Application

***Najwa Mohamad, Punitha Govintharaju**

Department of Pharmaceutical Sciences**,** Faculty of Pharmacy, University of Cyberjaya, Cyberjaya, 63000, Malaysia.

Email : najwa@cyberjaya.edu.my

Abstract

Sodium alginate (SA) and Carboxymethylcellulose (CMC), a cellulose derivative, has been used in wound dressing since it has good biocompatibility, hydrophilic, non-toxic and non-allergenic. This study is to develop and characterize CMC-SA based hydrogel as wound dressing material and also to incorporate Octenidine Dihydrochloride (OCT) as antimicrobial agent into the hydrogel and evaluate its release. The CMC-SA hydrogel was formulated using physical crosslinking method, and PEG was used as plasticizer. Following the formulation, the formulation was visually examined for several characteristics. Expansion study was conducted and Franz cell drug permeation study was done for the drug loaded hydrogel to determine the pattern of OCT release from hydrogel. The resulting hydrogel formulation was clear and, homogenous and showed a good expansion capacity up to 48 hours. 0.5% of OCT is incorporated into the hydrogel and a controlled release pattern was observed in CMC-SA based hydrogel. Based on the expansion study, the CMC-SA-OCT hydrogel is suitable to be used on highly suppurating wound but should be changed every 24 hours. This study has revealed that CMC-SA based hydrogel could be a promising wound dressing material in therapeutic applications and it can be used for highly suppurating wounds due to its characteristics.

Keywords: Carboxymethylcellulose, sodium alginate, hydrogel, wound dressing

1.0 Introduction

According to [1] it also have been demonstrated the effectiveness of providing moist environment to the wounds would help to promote healing of punctured wounds, damaged tissues and also burnt skin tissues. It was demonstrated that the process of healing of a wound is faster when a wet dressing as provided by hydrogel instead of a dry dressing [2]. Classification of wound dressing is based on functioning mechanism of hydrogel, primary, secondary, island , traditional and modern dressing respectively [3]. It has been reviewed by Jones in a study, the shortcomings due to the use of the traditional dressing [4]. Modern dressings that has been improved and developed is able to sustain and provide a moisture environment to promote a better

healing effect of the wound. Modern dressings are categorised based on their materials, such as hydrocolloids, alginates and hydrogels, and the formulations are usually gels, thin films and foam sheets [3].

Hydrogels are swollen three-dimensional(3D) networks of hydrophilic polymers which is held together by bonds and forces. This is one of the reasons, hydrogels are choice of material for controlled release application. Hydrogels has soft tissue biocompatibility, making it easy for dispersion of drugs in the matrix, and its maximum level of control can be reached by choosing the precise and appropriate properties of polymer network[5]. Cellulosic compounds such as hydroxyalkyl cellulose and carboxymethylcellulose (CMC) are primarily used for wound dressings. Moreover, adding methylcellulose, a water soluble polymer to the dressing material could enhance and control the drug release [6].Sodium alginate ($NaC_6H_7O_6$) is a linear polysaccharide derivative of alginic acid comprised of 1,4-beta-D-mannuronic acid and alpha-L-guluronic (G) acids [7]. Alginates are primarily used as absorbing wound dressings thus it is chosen to be suitable material for drug delivery system[8]. The use of alginates as dressing material is mainly due to their high absorbency, thus their ability to form gels upon coming into contact with wound exudates [3]. While antibiotics has issues of resistance which acts as a barrier for their wide therapeutic use, antiseptics which has unspecific modes of action are highly unlikely to result in resistance. They are topically used to reduce the risk of colonization or transmission of pathogens, as well as minimising the risk of infection, and also treat infections[9].

2.0 Experimental

2.1 Materials

Sodium alginate powder purchased from Chemiz, Malaysia. Carboxymethylcellulose (CMC) powder purchased from R&M Chemicals, UK. Polyethyleneglycol (PEG) manufacture by R&M Chemicals, UK. Octenidine Dihydrochloride manufactured by Toronto Research Chemicals Inc., Canada. Fish gelatin powder manufactured in Alpha Chemika, India. Phosphate buffer saline tablets manufactured by Fisher BioReagents, Belgium. Cellulose acetate membrane by Sartorius Stedim Biotech, Germany.

2.2 Preparation of Hydrogel Film

Method of preparation of aqueous carboxymethylcellulose(CMC) solution was adapted and modified from[10] and method of preparation of sodium alginate was adapted from from[11]. 6.0 g of carboxymethylcellulose (CMC) was dissolved in 100ml distilled water, stirred using magnetic stirrer or glass rod, and 8.0 g of sodium alginate was added into the CMC solution and stirred together until homogenous[10]. 6.0g of PEG was added and stirred until homogenous. 20ml of the resultant gel was poured into a petri dish and dried in the oven at 40̊ C for 7 days[11].

2.3 Drug Loading

Drug loading method was adapted and modified from[5]. Drug loaded hydrogels were formulated by dispersing the homogenous gelling agents slowly in an aqueous based solution containing OCT 0.5%. 6.0g of PEG is added and stirred using a glass rod until homogenous. The resulting mixture was then evenly spread on a petri dish and hot-air dried in an oven at 40°C.

2.4 Physicochemical Evaluation And Characterization Of The Prepared Hydrogels

2.4.1 Visual Examination

The visual examination is carried out based on the methods in [5]. Hydrogels was evaluated visually for their colour, homogeneity which includes the appearance and presence of any aggregation. It also inspected for its grittiness (presence of any solid particles) and syneresis (phase separation) [5].

2.4.2 Expansion Study

The expansion study is adapted and modified from [11]. Expansion study was performed on a gelatin medium as the gelatin medium will the imitate wound surfaces. The gelatin medium was prepared using 4g of gelatin powder and 100 ml distilled water. The gelatin powder is dissolved in 100 ml of distilled water at 90°C and stirred until a clear solution is formed. Then, 25g of the formed clear gelatin solution poured into glass petri dishes and it is allowed to cool to room temperature (25°C) overnight. Then, 1cm diameter films was cut and placed on the gelatin surface. Any change in diameter at time intervals of every 1 hour (Dt) was measured for a period of 8 hours, and then at 24 hours and 48 hours. Expansion ratio was calculated using the following formula:-

Expansion = [diameter of sample at time t (Dt) /diameter of sample at time 0 (Do)] [11].

2.4.3 Franz Cell Drug Permeation Study

Drug permeation studies of model drug liberating from dried films will be investigated using Franz diffusion Cell System (Permegear. Inc., USA). A clean, dried receptor cell was filled with phosphate buffer solution (PBS) at pH 7.4 and it is then allowed to equilibrate at 37°C. The cellulose acetate membrane with pore size of 0.45mm was mounted between receptor and donor compartment. Then film then placed above the cellulose acetate membrane and sandwiched between receptor and donor compartments. The temperature of the receptor compartment was assured to be maintained at 37°C with circulating water jackets throughout the entire experiment. All openings including donor top and receptor arm was occluded with parafilms. This is done to prevent any evaporation. Then, using a glass syringe, the volume of 0.5 ml samples was withdrawn from the receptor medium at regular time intervals for 8 hours and the receptor volume was kept constant by

replacing equal volume of fresh PBS solution of 37°C. The samples were measured by using UV spectrophotometer [11] at 285nm[12].

2.5 Data analysis

All values are expressed as mean ± SD. Statistical evaluation was done using independent T-test and One Way ANOVA and Post Hoc test to test for any significant difference between the means using Statistic Package for Social Sciences programme version 23 (IBM SPSS 23.0,2017). The level of significance were set at $p<0.05$.

3.0 Results and discussion

3.1Preparation of Hydrogel

A few formulations was formulated for the hydrogel preparations. Formulation was tried 2g, 3g, 4g, 5g and 10g of gelling agents respectively in 100 ml of distilled water. For most of the formulations, the PEG amount was kept constant. The summary of the weight of gelling agents used in each formulations are shown in Table 3.1.

Table 3.1 : Amount of gelling agents used in each formulations (F1-F15)

Formulation	CMC(g)	SA(g)	PEG(g)	Total (g/100ml)
F1	0.9	0.9	0.2	2
F2	1	1	1	3
F3	1.2	0.2	0.6	3
F4	2	1	1	4
F5	1	2	1	4
F6	2	2	1	5
F7	1	3	1	5
F8	3	1	1	5
F9	8	1	1	10
F10	2	7	1	10
F11	1	3	2	6
F12	1	3	3	7
F13	1	3	4	8
F14	5	7.5	5	17.5
F15	6	8	6	20

F1 – F8 (Figure 3.1) was left at hot air oven at 37̊C for 72 hours and they were still in a liquid form after 72 hours. They showed no improvement or any development into becoming hydrogel. All formulations looked almost the same. F9 (Figure 3.2) and F10 (Figure 3.3) was too viscous and was hard to stir and had to be stirred manually using glass rod. The formulation was still viscous fluid after 72 hours and it was still sticky and hydrogel film was not developed as well. However, after 7 days in the oven at 40̊C, F9 (Figure 3.2) was thin, dry and brittle plastic like film. F10 developed into a thick, strong plastic like film and was dry.F11 - F13 showed no development until day 7, and the temperature was increased on the end of day 7 and they developed to become a film on Day 8. In general, the film was dry, plastic like and flexible film. The film was fragile and can be torn. There was also no significant visible visual difference between the films. F11 was dry, was flexible, but brittle and fragile, and it can be torn apart easily. F12 on the other hand, plastic like and was brittle, and it can be torn like a paper when exert a little bit of force, yet flexible. F13, was flexible, it was easily peeled from the petri dish, was flexible but it was plastic like too and it was too dry but it cannot be torn apart with the same force used for F12. Thus, the F13appeared to be greater in strength among all 3 formulations physically and also visually. Despite the brittleness and the fragility, there is no other significant visible differences among these formulations.F14 (Figure 3.4) was left to dry in hot air oven at 40̊C for 7 days, and the formulation was half dry and half was still gel-like and has not dried. The part that has dried, can be peeled off the petri dish and it did not stick to the petri dish, while the undried part was sticking to the petri dish, especially the bottom part is very gel-like. F15 (Figure 3.5)had developed into a hydrogel film, it had dried well, and can be peeled off the petri dish easily. This was a successful formulation out of the 15 formulations.

All the formulations was clear and homogenous and showed no syneresis or grittiness.

3.2 Drug Loading Into Hydrogel Formulation

Another formulation similar to F15 is formulated as F16, and 1% OCT was incorporated into the hydrogel and the formulation became very foamy upon stirring and there was undissolved particles in it. Heat was used initially to dissolve the drug in distilled water. The resulting solution was put in a petri dish and left to dry, and after 7 days at 40̊C, it became a white coloured dry film. It was dry, can be peeled off from the petri dish easily, yet was very fragile and can be broke apart. Next in F17 (Figure 3.6), 0.5% of OCT was incorporated and no heat was used for this formulation and the hydrogel was formed with adequate flexibility. Thus, this formulation was used for further evaluation such as expansion study and drug release.

F16 was absolute white, and it was not homogenous with presence of clumps and gritty texture. F17 on the other hand, was clear, transparent and a hydrogel was formed with homogeneity with absence of syneresis and grittiness.

3.4 Expansion study

The summary of the expansion study results are as tabulated in Table 3.2 and a visual representation of the results is shown in Figure 3.12.

Table 3.2 Result of expansion study of drug unloaded and drug loaded hydrogel

Time	Diameter of sample (Dt)	
	Drug unloaded hydrogel	Drug loaded hydrogel
0 (D0)	1.000	1.000
1	1.400 ± 0.000	1.267 ± 0.058
2	1.400 ± 0.000	1.367 ± 0.058
3	1.600 ± 0.000	1.433 ± 0.058
4	1.600 ± 0.000	1.467 ± 0.058
5	1.700 ± 0.058	1.567 ± 0.058
6	1.900 ± 0.000	1.567 ± 0.058
7	1.933 ± 0.058	1.600 ± 0.000
8	1.933 ± 0.058	1.600 ± 0.000
24	1.933 ± 0.058	1.600 ± 0.000
48	2.033 ± 0.058	1.600 ± 0.000

Notes : Values expressed as mean ± SD, n=3 in each group. Significance values were according to Independent T-test

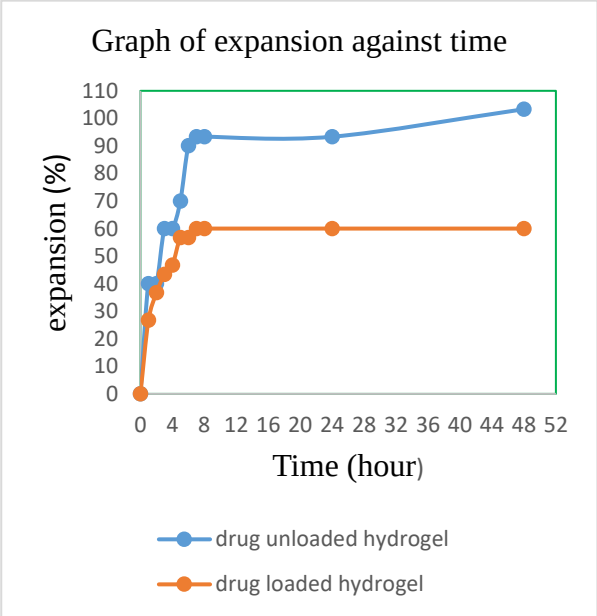

Figure 3.12 Graph of expansion against time for expansion study of drug unloaded and drug loaded hydrogel

The drug unloaded hydrogel hydrates faster than the drug loaded hydrogel. It expanded 40% of its original size within first hour. It was also observed that the drug unloaded hydrogel retained their shape throughout, up to 48 hours. The hydrogel expanded up to 103 ± 0.06% in 48 hours. The hydrogel retained its length from the 7th hour to 24 hours and again showed some increase in length on 48th hour. It retained its shape longer than the drug loaded hydrogel. On the other hand, within the first hour the drug loaded hydrogel expanded 26.67% of its original length which is lesser compared to the drug unloaded hydrogel. After 7th hour, the hydrogel has expanded to 60% of its original size and did not expand further and also lost is shape slightly on the sides. The expansion values for both drug loaded hydrogel and drug unloaded hydrogel was significantly different ($p < 0.05$) throughout the study period up to 48 hours.

3.5 Franz Cell Drug Permeation Study

The standard curve as shown in Figure 3.11 was constructed for OCT drug release. The equation is expressed as (y= 0.0067x + 0.0027) with R^2 = 0.9959. This standard curve was used as a reference standard for the study of release of OCT drug from the hydrogels. The R^2 value shows a good relationship between the concentration and absorbance. Franz cell drug release studies were performed to compare the drug release profiles from CMC-PEG-OCT hydrogel, SA-PEG-OCT hydrogel and CMC-SA-PEG hydrogel. Drug release profile was shown in terms of cumulative amount over 8 h.

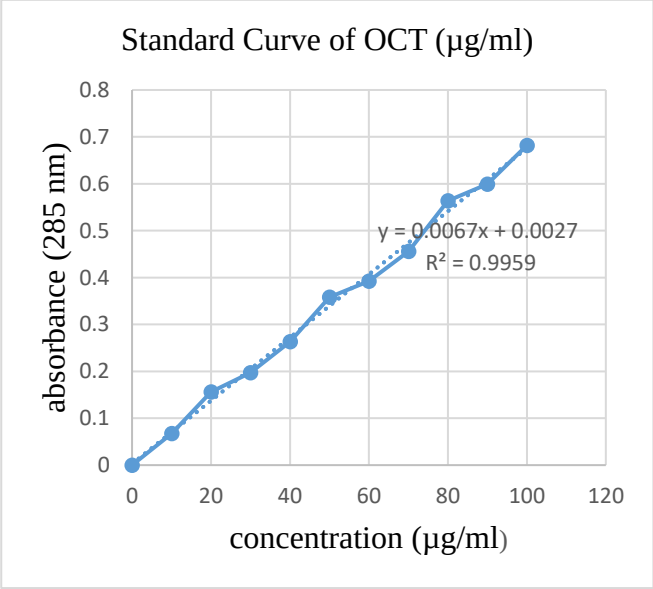

Figure 3.13 The standard curve of OCT measured at 285 nm with various concentration (0-100µg/ml).

The concentration of OCT release (μg/cm^2) per hour is expressed in table 3.7 below.

Table 3.7 Cumulative concentration of OCT release SA-PEG-OCT hydrogel, CMC-PEG-OCT hydrogel and CMC-SA-PEG-OCT hydrogel over period of 8 hours(μg/cm²)

Time	Cumulative concentration of OCT release (μg/cm²)		
	cmc	sa	cmcsa
1	6.263 ±0.086^{bcdefgh}	14.1243 ±0.173^{bcdefgh}	5.866 ±0.000^{bcdefgh}
2	18.000 ±0.149^{adefgh}	21.980 ±0.376^{acdefgh}	8.647 ±0.345^{acdefgh}
3	23.468 ±0.228^{adefgh}	29.935 ±0.705^{abdefgh}	13.667 ±0.311^{abdefgh}
4	74.707 ±0.736^{abcefgh}	44.259 ±0.621^{abcefgh}	20.179 ±0.395^{abcefgh}
5	122.363 ±1.252^{abcdfgh}	63.706 ±0.971^{abcdfgh}	22.861 ±0.376^{abcdfgh}
6	167.109 ±4.362^{abcdegh}	85.243 ±1.268^{abcdegh}	34.647 ±0.431^{abcdegh}
7	182.427 ±4.461^{abcdefh}	123.795 ±1.268^{abcdefh}	37.976 ±0.376^{abcdefh}
8	196.203 ±4.597^{abcdefg}	169.312 ±1.044^{abcdefg}	39.911 ±0.448^{abcdefg}

Notes : Values expressed as mean ± SD, n=3 in each group. Significance values were according to One-way ANOVA (Post-Hoc test).

[a] is significant when compared to other hydrogels at hour 1 ($p<0.05$)

[b] is significant when compared to other hydrogels at hour 2 ($p<0.05$)

[c] is significant when compared to other hydrogels at hour 3 ($p<0.05$)

[d] is significant when compared to other hydrogels at hour 4 ($p<0.05$)

[e] is significant when compared to other hydrogels at hour 5 ($p<0.05$)

[f] is significant when compared to other hydrogels at hour 6 ($p<0.05$)

[g] is significant when compared to other hydrogels at hour 7 ($p<0.05$)

[h] is significant when compared to other hydrogels at hour 8 ($p<0.05$)

According to ANOVA test, there is significant difference between the three hydrogels ($p<0.05$).

The concentration of OCT release from hydrogel is visually expressed in Figure 3.14 as follows.

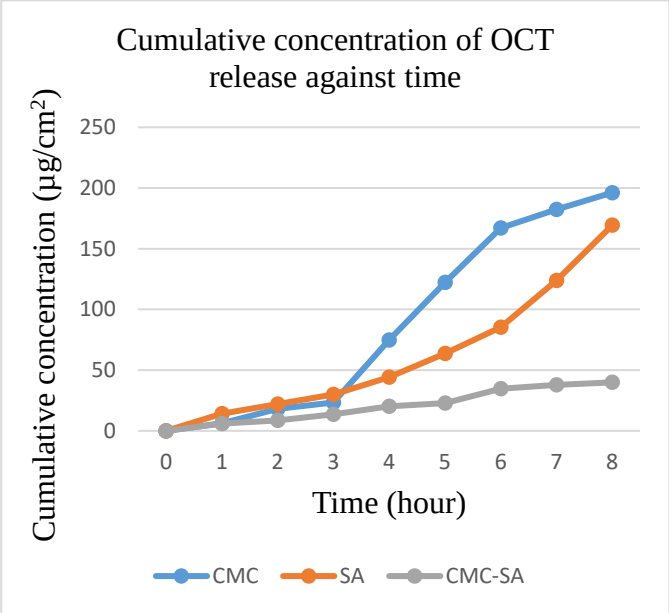

Figure 3.14 Cumulative amount of OCT release from SA-PEG-OCT hydrogel, CMC-PEG-OCT hydrogel and CMC-SA-PEG-OCT hydrogel over period of 8 hours.

CMC-PEG hydrogel shows a steady increase in the OCT drug released amount in the first 3 hours followed by a dramatic and extensive increase in the released amount of drug in the next 3 hours up to 6th hour and the release shows a steady trend again up from the 6th hour to 8th hour. Meanwhile, SA-PEG-OCT hydrogel shows steady release of drug OCT from the hydrogel over the test period of 8 hours. On the other hand, CMC-SA-PEG-OCT hydrogel shows a consistent rise in the amount of drug OCT release from the hydrogel over 8 hours.

The cumulative amount of OCT released over 8 hours for CMC-PEG-OCT hydrogel, SA-PEG-OCT hydrogel and CMC-SA-PEG-OCT hydrogel is 196.203 ± 4.60 µg/cm^2, 169.312 ± 1.04 µg/^{cm} and 39.911 ± 0.45 µg/cm^2 respectively.

Therefore the total amount of OCT released from CMC-PEG-OCT hydrogel (196.203 ± 4.60 µg/cm^2) is the highest of the three compared hydrogels. the total amount of OCT release from SA-PEG-OCT hydrogel (169.312 ± 1.04 µg/cm^2) is slightly lower than that of CMC-PEG-OCT hydrogel. Meanwhile, the CMC-SA-PEG-OCT hydrogel (39.911 ± 0.45 µg/cm^2) shows the least total amount of OCT released from the hydrogel.

4.0 Discussion

4.1 Preparation of Hydrogel

Hydrogels are crosslinked polymers, which can swell considerably in aqueous medium without dissolution. Crosslinks within polymeric hydrogels can be created either chemically or physically. The use of crosslinking

agents to chemically form polymeric hydrogels may lead to toxic side effects or cause any unwanted reactions with incorporated drugs[13]. Therefore, drug encapsulation using alginate is often carried out physically by dispersion of the alginate or drug solution into a gelation medium[14]. Furthermore, Na-CMC, a cellulose derivative, has been used in wound dressing since it is good biocompatibility, hydrophilic non-toxic and non-allergenic. Generally, the formation of specific intermolecular interactions through hydrogen bonding between two or more polymers is responsible for the observed mixing behaviours and properties of the blends prepared from aqueous solutions. The properties of resulting blends can be studied to explore further applications for biomedical and pharmaceutical devices. Because both SA and CMC are water soluble polymers, they are compatible polymers due to the formation of hydrogen bonds [15]. However, there is optimum degree of crosslinking to obtain a relativelystrong, yet elastic hydrogel with desired characteristics [16]. Thus, this could be a reason on why the first 8 formulations was not formed as a hydrogel but remained as fluids as there is no optimum crosslinking was achieved to obtain an elastic and desired hydrogel.This is probably because too little gelling agents was used in the formulations that could not create physical networks to form a hydrogel.

As for F9 and F10, it developed into films, but plastic like film may be due to insufficient amount of PEG for the flexibility and there is imbalance amount of both gelling agents (CMC and SA).

The hydrogels made from higher molecular weight PEG of more than 3000 have significant and useful properties. Using them, it is possible to provide a hydrogel that enables delivery of most drugs over periods of more than 16 hours[17]. This justifies the use of PEG 4000 in the formulations. On F11, F12 and F13, only the PEG weight was manipulated and they showed differences on the characteristics of the formulations. The lesser PEG concentration used, the more brittle the formulation was. And the more PEG concentration used, the hydrogels appears to be stronger visually and physically. Regarding to the addition of polyethylene glycol (PEG) to produce hydrogel blends, according to [18] in one of the studies, it was observed that PEG has shown improvement on the chemical stability of the hydrogels as the degradability was reduced as well as PEG act as bridging agent between CMC polymer chains, which enhances the crosslinking effect. This explains the increasing trend of stability and strength among the F11, F12 and F13 where as the PEG weight was used at 2g, 3g and 4g respectively.

As for F14 and F15. More SA is used than CMC because comparing the earlier formulations such as for F11, F9 and F10. The formulation that contained more SA was much more promising to develop into a hydrogel. Comparing F8 CMC:SA:PEG (3:1:1) and F11 CMC:SA:PEG (1:3:2) , F11 was developed into a film where as the F8 was still a solution.

Thus, this explains on why more SA is used in F14 and F15 and the ratio of CMC:SA:PEG was manipulated, and as more PEG is used, F15 was more flexible and formed into a hydrogel ,while the F14 may have insufficient amount of PEG, thus it could not produce a solid flexible hydrogel but formed a gel kind of formulation instead.

4.2 Drug Loading

Unlike antibiotics, OCT is only suitable for topical use. It has been approved as one of the medicinal substance used for skin, mucous membrane and wound antisepsis. On a first glance, this might seem to be a drawback to systemically available antibiotics, but it is not because local therapy with antibiotics often leads to microbial resistance, intolerability, toxic side effects and sensitization. While OCT is well tolerated and does not induce resistance. This is well discussed by[9] in a study.

The F16 was formulated with drug loading with 1% of OCT. This formed a foamy solution upon stirring. This could be due to the use of heat during the solubilisation of the OCT.

Thus in the next formulation, F17, the heat was not used to dissolve the OCT and the percentage of the drug was reduced to 0.5%. In a study by [19] , 0.5% of OCT has been used for active wound dressing preparation, thus this concentration is believed to produce an positive effect of the wound surfaces and used in this study. Upon removing the involvement of heat in the dissolving process of the drug, the foamy solution was not formed during stirring and incorporating the drug into the gelling agent.

4.3 Expansion Study

Gelatin medium was used in the study to evaluate the expansion of the hydrogel. This is because, as discussed by[20]in a study, gelatin medium provides water producing substrate and it resembles a suppurating wound which is highly moist. A gelatin model, appears to a quick and trustable quality control method for evaluating in quantity the differences in flow properties, hydration as well as the expansion properties of the dried formulations in a highly moist environment. From this study it is seen that the expansion limit for the drug loaded hydrogel is only up to 60% and the hydrogel loses it shape on its side after 24 hours.

The OCT unloaded hydrogel expanded up to 103% and did not show any rupture at any point throughout the expansion study period up to 48 hours. It could retain its shape throughout. This might be due to their mechanical strength as mentioned by[21] that SA-CMC blends have good mechanical and thermal properties.

From this study, it was postulated that CMC-SA-PEG-OCT hydrogel is not suitable for medium to heavy suppurating wound beyond 24 hours because the film able to revert to gel form when in contact with biological fluid that is produced from the highly suppurating wound. It is noted that the transformation of the hydrogel’s texture to the gel form may lead to formation of gummy residue deposited in and around the wound area. This will make dressing process to be unfavourable as it is difficult to remove the dressing from

the wound area and the residue of dressings will need to be rinsed out with normal saline, making the changing procedure laborious and time-consuming[11]. Thus, the CMC-SA-PEG-OCT hydrogel should be changed from the wound every 24 hours.

4.4 Franz Cell Drug Permeation Study

Franz cell drug release studies were also performed to compare drug release profile among the CMC-PEG-OCT hydrogel, SA-PEG-OCT hydrogel from another study and CMC-SA-PEG-OCT hydrogel (Formulation 17). With the increase in content of CMC, the cumulative release increased as mentioned by[22], thus the cumulative amount released was the most for the CMC-PEG-OCT hydrogel where it has more CMC (20g of CMC) compared to SA-PEG-OCT hydrogel and CMC-SA-PEG-OCT (6g of CMC) hydrogel.

All 3 hydrogels showed a steady release of OCT in first 3 hours. However, it is seen that SA-PEG-OCT hydrogel have greater OCT release rate compared to CMC-PEG-OCT and CMC-SA-PEG-OCT hydrogel over 3 hours. This may be due to greater crosslink density of CMC-PEG-OCT hydrogel compared to SA-PEG-OCT hydrogel[23].

OCT release from SA-PEG-OCT hydrogel continue to increase steadily over next hours up to 8 hours, yet in lesser concentration that CMC-PEG-OCT hydrogels.

On the other hand, OCT release from CMC-PEG-OCT hydrogel showed sudden increase up to 6 hours and the showed a steady increase from 6^{th} hour to 8^{th} hour. The sudden increase in the release of OCTmay be due to the breakdown of the hydrogel, and this has been discussed in the expansion study of this CMC-PEG formulation where as the hydrogel dissolved in the gelatin medium at the 5^{th} hour.

This causes more drug to be released as according to [24], who mentioned that influx of water dilutes the polymer below its critical gelation concentration and the matrix will lose its gel-like properties. As more water enters the hydrogel, this will eventually lead to rupture of the physical structure of hydrogel and this will cause more drug to be release at a point of time. This could justify the sudden increase in the drug release from 3rh hour to 6^{th} hour. Another reason for this dramatic increase in drug release according to [24] is maybe due to high water content of the CMC-PEG-OCT hydrogel. As mentioned in the study, high water content of most hydrogels results in relatively rapid release of drugs from the gel matrix over period of time.

For CMC-SA-PEG-OCT hydrogel, it showed a controlled release of OCT over 8 hours. One of the approach used for controlled drug release from hydrogels is by creation of chemical bonds between the drug and the polymer chains. Covalent linkages that is formed between the drug and polymer would immobilize the drug, and can be either highly stable or cleavable. Highly stable covalent linkages retain the drug until the network degrades, thus the release is interrupted and happens in a very slower manner. Cleavable covalent linkages, much like cleavable crosslinks in degradable networks, can be designed to cleave over time or in response to

environmental factors and sensitivity. The drugs are released at a rate determined by the cleavage of linkers. Strategies of linkers cleavage include the formation of amide bonds and the use of long-chain polyethylene glycol (PEG) linkages[25].

Since the CMC-SA-PEG-OCT hydrogel showed a controlled rise in the drug release, even with the least cumulative concentration, this formulation might be the most suitable for wound care because according to [11] it had been revealed that slow release of drugs from polymeric medicated dressings offer some potential advantages which generally includes prolonging the action of the active drug over longer periods of time. This is done by allowing continual release of drugs from a dosage form. It had been also discussed that the wound care products which release a therapeutic material to a wound in a slow release manner for a longer period of time could improve the patient compliance by reducing the problem encountered with frequent dressing changes. Thus the present drug release study implied that by using the CMC-SA-PEG-OCT hydrogel which retain the drug for a longer period of time, thus minimise the dressing changing frequency.

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