ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

# Formulation and evaluation of Diclofenac sodium mucoadhesive buccal tablets by using natural polymers

Venkatalakshmi Raganathan*[1], Muhammad Zulfahmi Bin Abd Majid[1], Prasanthi Sri[1], Sasikala Chinnappan[2]

[1]Faculty of Pharmacy, Department of Dosage Form Design, MASHA University- Jalan SP 2, Bandar Saujana Putra, 42610 Jenjarom, Selangor, Malaysia
[2]Faculty of Pharmaceutical Sciences, UCSI University, Jalan Menara Gading 1, Taman Connaught, 56000 Kuala Lumpur, Wilayah Persekutuan Kuala Lumpur, Malaysia

*Article History:*

Received on: 25.11.2017
Revised on: 14.02.2018
Accepted on: 24.02.2018

*Keywords:*

Diclofenac sodium
First-pass hepatic metabolism
Mucoadhesive buccal tablet
*Ex vivo* mucoadhesion time

ABSTRACT

Diclofenac sodium is a common and widely-used drug for the treatment of pain, inflammation and also migraine. Unfortunately, it undergoes extensive first-pass hepatic metabolism when administered through the oral systemic route. Thus, this study will be about the formulation of mucoadhesive buccal tablets of diclofenac sodium that can prevent the extensive metabolism of the drug, which in turn increases its bioavailability inside the systemic circulation. This formulation might also reduce the dosing frequency, which can lead to a better patient compliance to the medication. The formulations would be using natural polymers such as acacia gum and chitosan as the mucoadhesive polymers. Ethylcellulose (EC) was included as the backing layer of the buccal tablets, along with other excipients. In total, four different formulations were prepared with the varying concentration of the natural polymers. The formulated buccal tablets have been evaluated for their general appearance, thickness, hardness, weight variation, friability, *ex-vivo* mucoadhesion time and other *in-vitro* tests such as swelling and dissolution studies. The finding of this study confirmed that Formulation 3 (F3) had the best properties of mucoadhesive buccal tablets as it displayed the highest *in-vitro* swelling index and *in-vitro* dissolution profile, also with the longest *ex-vivo* mucoadhesion time.

* Corresponding Author

Name: Dr.Venkatalakshmi Ranganathan
Phone: +060163747705
Email: rvenkatmpharm@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v9i1.1253

Production and Hosted by

IJRPS | https://ijrps.com


## INTRODUCTION

Diclofenac sodium is a widely used non-steroidal anti-inflammatory drug (NSAID) mainly due to its antipyretic, analgesic and anti-inflammatory actions. It is commonly available in the form of sodium salt. Diclofenac sodium can also help in recovering from fever. It is usually indicated for treatments that requires a strong dose of pain relief such as migraine, post-operative pain and its prophylaxis, renal colic, rheumatoid arthritis and also acute gout.

Although it is effective in subsiding pain and inflammation, the amount of diclofenac sodium that actually circulates in the body after its admission is considered to be quite low. This is due to the fact that it undergoes first-pass metabolism in the kidney as the common route of administration for diclofenac sodium is by the oral systemic route (Balaji A., *et al*., 2014). It is known that the drugs delivered by the buccal mucosa route are free from degradation by the stomach acid and also the first-pass metabolism effect. (Abu-Huwaij *et al*., 2012).

Thus, this study is conducted in order to investigate the effectiveness of the buccal dosage form in avoiding the first-pass metabolism effect of

**Table 1: Formulations of the mucoadhesive buccal tablets**

| Ingredients (mg) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Diclofenac sodium | 20 | 20 | 20 | 20 |
| Acacia gum | 20 | - | 40 | - |
| Chitosan | - | 20 | - | 40 |
| Ethylcellulose + Brilliant Blue | 50 | 50 | 50 | 50 |
| Mannitol | 102 | 102 | 82 | 82 |
| PVP-K30 | 6 | 6 | 6 | 6 |
| Magnesium stearate | 2 | 2 | 2 | 2 |
| Total | **200** | **200** | **200** | **200** |
| Ratio (drug:polymers) | **1:1:0** | **1:0:1** | **1:2:0** | **1:0:2** |

**Table 2: The classification of drug transport mechanism based on release exponent**

| Release Exponent (n) | Drug Transport Mechanism |
|---|---|
| 0.5 | Fickian diffusion |
| 0.49 < n < 0.89 | Non-Fickian diffusion |
| 0.89 | Case II transport |
| n > 0.89 | Super case II transport |

diclofenac sodium, as well as increasing the bioavailabilty and also reducing dose frequency by its sustained or controlled drug release.

## MATERIALS

Diclofenac sodium, acacia gum, chitosan was purchased from Sigma-Aldrich (US). Ethylcellulose, mannitol, PVP-K30 (polyvinlypyrollidine), magnesium stearate and brilliant blue was purchased from R&M Chemicals (India). All other chemicals were used analytical grade.

## METHODS

### Construction of calibration curve

A stock solution of diclofenac sodium was prepared by dissolving 10 mg of the drug with 100 mL phosphate buffer solution of pH 6.8. Further dilutions of 10, 20, 30, 40, 50 and 60 µg/mL were prepared from the stock solution. All of them were then analysed by the UV-visible spectrophotometer at 276 nm. The results are shown in table 3 and figure 4. (Ahmed S.F *et al*., 2014).

**Table 3: The diclofenac sodium calibration readings**

| Concentration (µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.432 |
| 20 | 0.818 |
| 30 | 1.041 |
| 40 | 1.601 |
| 50 | 1.839 |
| 60 | 2.055 |

### Formulation of mucoadhesive buccal tablets by direct compression

Firstly, the active ingredient was mixed homogeneously with the natural polymers and excipients in a mortar. The mixed preparation was added first into the die of the single tablet compression machine. Later EC mixed with some brilliant blue was to form the backing layer. The compression formed a bilayer tablet of distinct colours. The formulation is shown in table 1. (Alanazi F.K *., et al*., 2007)

### Evaluation of mucoadhesive buccal tablets

(Cafaggi, S *et al*., 2006)

### Fourier Transform Infrared (FTIR) Spectroscopy

The drug and natural polymers interactions were analysed by the FTIR spectrophotometer (PerkinElmer, USA). The pure drug, the buccal tablet containing polymers were crushed and analysed by FTIR spectrophotometer to determine any interactions between the polymer and drug. (Ahmed S.F *et al*., 2014)

### General appearance

The tablets from all four formulations were evaluated for their shape, colour and surface texture. The observations were then recorded.

### Thickness

Three tablets from each different formulation were collected and the thickness of each tablets was measured by using a Vernier calliper. The average thickness was calculated and recorded.

### Hardness

Three tablets from each different formulation were collected and their hardness was tested by using the Monsanto hardness tester. The average hardness was calculated and recorded.

**Table 4: General appearances of the tablets in all four formulations**

| Formulation | Shape | Colour | Surface texture |
|---|---|---|---|
| F1 | Circular | Whitish mucoadhesive layer, bluish backing layer | Smooth |
| F2 | Circular | Whitish mucoadhesive layer, bluish backing layer | Smooth |
| F3 | Circular | Whitish mucoadhesive layer, bluish backing layer | Smooth |
| F4 | Circular | Whitish mucoadhesive layer, bluish backing layer | Smooth |

**Table 5: Evaluation characteristics of the different formulations**

| Formulation | Thickness (mm)(n=3) | Hardness ($kg/cm^2$)(n=3) | Weight variation (g)(n=10) | Friability (%) (n=10) |
|---|---|---|---|---|
| F1 | 9.49 ± 0.12 | 4.3 ± 1.47 | 0.21 ± 0.01 | 0 |
| F2 | 9.56 ± 0.02 | 4.1 ± 0.06 | 0.23 ± 0.02 | 0 |
| F3 | 9.53 ± 0.03 | 7.1 ± 0.7 | 0.20 ± 0.02 | 1 |
| F4 | 9.56 ± 0.01 | 3.9 ± 0.06 | 0.20 ± 0.01 | 0 |

**Table 6: The overall in vitro swelling index profile for all formulations**

| Time (mins) | Swelling index (%) | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 0 | 0 | 0 | 0 | 0 |
| 5 | 4.8 | 2.3 | 8.2 | 3.5 |
| 10 | 8.1 | 4.8 | 15 | 5 |
| 15 | 12.2 | 7.88 | 19 | 8.2 |
| 20 | 17.6 | 11.5 | 25 | 12.2 |
| 25 | 23.3 | 16.5 | 30 | 18.5 |

**Table 7: The overall *in vitro* drug dissolution profile**

| Time (hrs) | Drug dissolution (%) | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 0.5 | 24.6 | 18.6 | 31.6 | 20.3 |
| 1 | 35.8 | 26.2 | 46.6 | 30.9 |
| 2 | 47.9 | 36.1 | 57.7 | 47.2 |
| 3 | 51.6 | 47.7 | 64.5 | 51.2 |
| 4 | 65.2 | 58.5 | 77.9 | 60.4 |
| 5 | 73.3 | 72.6 | 84.2 | 75.2 |
| 6 | 85.5 | 80.1 | 87.3 | 82.3 |

**Table 8: The data representation of regression value, R2 and release exponent, n-value**

| Formulation | $R^2$ value | | | n-value |
|---|---|---|---|---|
| | Zero order model | First order model | Higuchi's model | Korsmeyer-Peppas model |
| F1 | 0.9254 | 0.9539 | 0.9886 | 0.7337 |
| F2 | 0.9742 | 0.9752 | 0.9775 | 0.7301 |
| F3 | 0.8525 | 0.9822 | 0.9839 | 0.7511 |
| F4 | 0.9410 | 0.9700 | 0.9886 | 0.7385 |

**Weight variation**

Ten tablets from each different formulation were collected and the weight of each tablets was measured by using the electronic beam balance (Smith Scale Inc., USA). The average weight and the standard deviation had been calculated and recorded.

**Friability**

Roche type friabilator (Electrolab, India) was used to test 10 tablets from each different formulation on their resistance to shock and abrasion. The tablets were placed in the friabilator that revolves at 25rpm, dropping the tablets at the height of 6 inches with revolution. After 100 spins, the tablets had been weighed and the percentage loss was recorded by the formula,

$$F = \frac{W_{\$n\$\&\$a(} - W_{*\$na(}}{W_{\$n\$\&\$a(}} \times 100$$

***In vitro* swelling studies**

The tablets from each different formulation were weighed ($W_1$) and placed separately in petri dishes with 50 mL of phosphate buffer of pH 6.8. At the

 

time intervals of every 5 minutes, up until the 25th minutes the swollen tablets were removed and reweigh ($W_2$) again (Kaundal, A., *et al*., 2015). Then, the percentage hydration was calculated by,

Swelling index = $[(W_2-W_1)/W_1]$ X 100

in which, $W_1$: Initial weight, $W_2$: Final weight

### *In vitro* dissolution studies

The dissolution study was carried out by using the *in vitro* dissolution machine (Electrolab TDT-08L USP Dissolution Tester, India). The tablets from each different formulation were added into their respective bowls with 500 mL of phosphate buffer solution pH 6.8. All the stirring fans inside the bowls were set to 50 rpm USP. 5 mL of the solution from each basket containing the tablets were then collected at a specific time interval of 0.5 hour, 1 hour, 2 hours up until the 6th hour. The amount of drug released in the solution has been determined by the UV-visible spectrophotometer at 276 nm. (Juliano, C *et al*., 2008)

### *In vitro* drug release kinetic studies

The rate of drug release was studied by using different kinetic models. They are mathematically determined by using the zero order, first order, Higuchi and Korsmeyer-Peppas drug release kinetic models. Zero order drug release means that the rate of drug release is constant and independent to that of the concentration of the drug. If the mechanism of drug release follows the first order, it means that the rate of drug release depended on the concentration of the drug. For Higuchi's model, the rate of drug release is determined to be a diffusion process that follows Fick's Law. The last model which is the Korsmeyer-Peppas model determines the drug release pattern whether it is that of a hydrophilic matrix. Table 2 shows the classification of drug transport mechanism based on the value of the release exponent. (Giannola, I.G *et al*., 2007)

### *Ex vivo* mucoadhesion time studies

The *ex vivo* mucoadhesion time was carried out after employment of the tablets on a freshly cut goat buccal mucosa. Inside a beaker, a fresh goat buccal mucosa was fixed about 2.5 cm from the bottom. Mucoadhesive layer containing drug of each tablet was moistened with a drop of phosphate buffer (pH 6.8) and pasted to the goat buccal mucosa by employing a light force with a fingertip for 30 seconds. 200 mL of phosphate buffer (pH 6.8) was placed in a beaker and had been kept at 37 ºC ± 1 ºC. After 2 minutes, a 50 rpm stirring rate was employed to create the buccal cavity environment and the tablet adhesiveness had been observed. The time needed for the tablet to detach from the goat buccal mucosa was then recorded as the *ex-vivo* mucoadhesion time. (Munasur, A.P., *et al*., 2006)

## RESULTS AND DISCUSSIONS

### FTIR drug-excipients compatibility studies

The peaks formed on the spectra of diclofenac sodium were in range with the standard, which appeared at the wavelength of 1000 $cm^{-1}$ to 2000 $cm^{-1}$. The similar pattern of the spectra for the two formulations observed. It conferred no interactions have occurred. Diclofenac sodium was observed to be maintaining its identity throughout this experiment. The results are shown in fig 1-3.

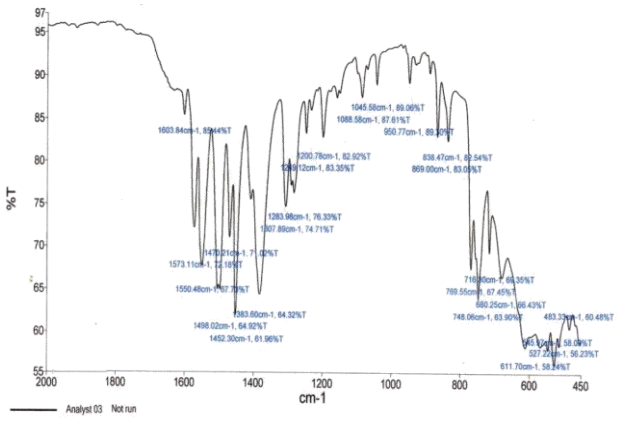


**Figure 1: FTIR Spectroscopy of the pure diclofenac sodium**

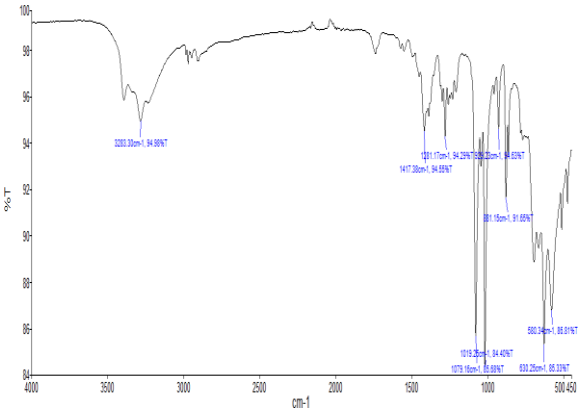


**Figure 2: FTIR Spectroscopy of the diclofenac sodium and acacia gum**

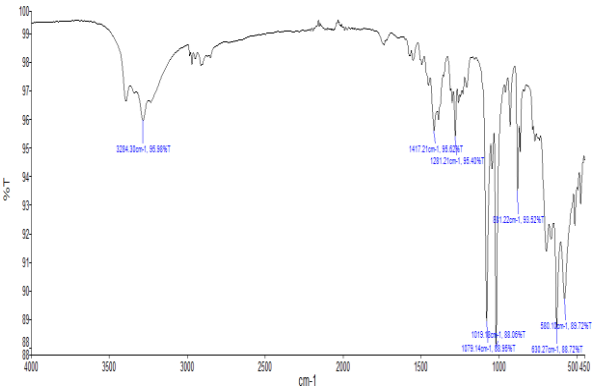


**Figure 3: FTIR Spectroscopy of the diclofenac sodium and chitosan**

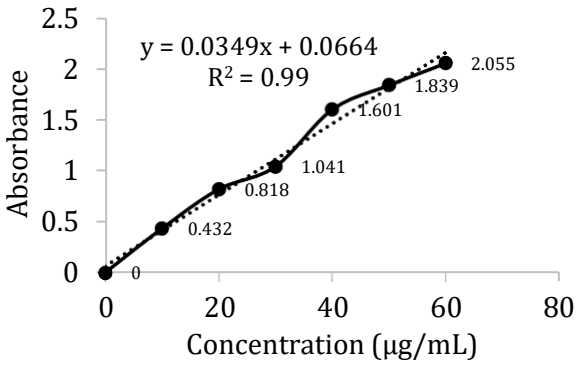


**Figure 4: The calibration curve of diclofenac sodium**

**Physicochemical evaluation of the mucoadesive buccal tablets**

**General appearance**

The general appearance of the formulated mucoadhesive buccal tablets from the different formulations were observed and recorded. The results are shown in in table 4.

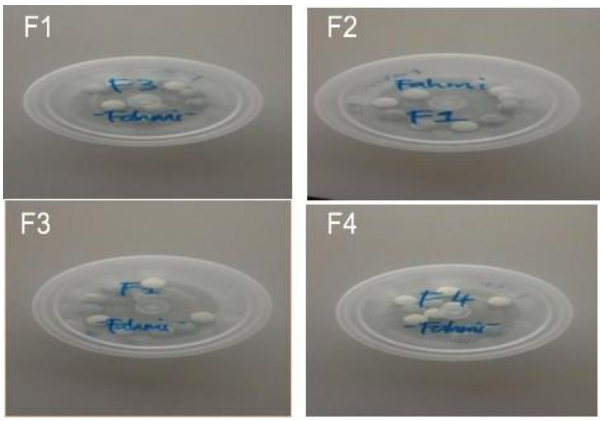


**Figure 5: The general appearances of mucoadhesive buccal tablets for the four formulations**

**Thickness**

All of the tablets have the thickness in the range of 9.49 mm to 9.56 mm. The uniformity of the tablets thickness was not affected by the type of natural polymers used. The results are shown in in table 4.

**Hardness**

The hardness ranged from 3.9 kg/cm$^2$ to 7.1 kg/cm$^2$. The hardest tablets came from F3 while the weakest one came from F4. This showed that the tablets formulated with increasing amount of acacia gum were much harder than those formulated using chitosan. The results are shown in in table 5.

**Weight variation**

The average weight of the tablets from ranged from 0.20 g to 0.23 g. The results are shown in in table 5.

**Friability**

All the tablets showed high tendency to withstand mechanical strength as the maximum percentage loss of friability is only at 1%. The results are shown in in table 5.

***In vitro* swelling studies**

From the study, it can be seen that there is an increasing trend on the degree of swelling displayed by all of the mucoadhesive buccal tablets. The highest swelling index was observed to be from the tablets of F3 and the minimal swelling index was seen from the tablets of F2. The results are shown in table 6 and fig 6.

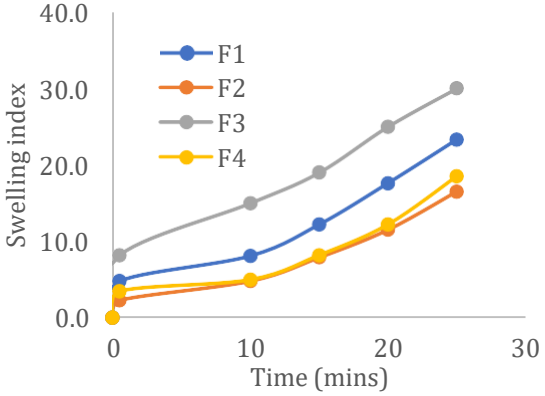


**Figure 6: The graph of *in vitro* swelling index profile**

***In vitro* dissolution studies**

From the test conducted, it can be observed that the rate of dissolution for the tablets in all formulations has an increasing pattern of drug release profile. Among of all the formulations, it was determined that the tablet in F3 had the highest rate of drug dissolution and release as it can reach 87.3%, the best drug release percentage in the test at the 6$^{th}$ hour. All the formulations were considered to have a good drug release profile as they achieved more than 80% for the rate of drug dissolution and release. The results are shown in table 7 and fig 7.

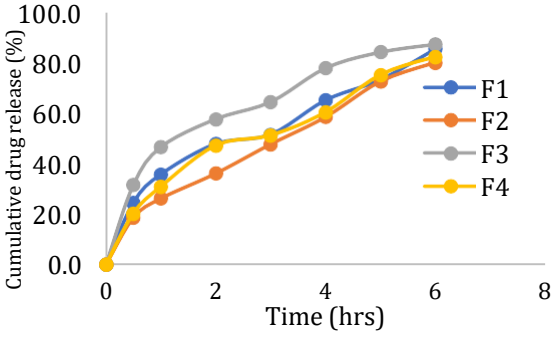


**Figure 7: The *in vitro* drug dissolution index profile**

### *In vitro* drug release kinetic studies

The drug release kinetics was determined by using the mathematical method of zero order model, first order model, Higuchi's model and Korsmeyer-Peppas model. The rate of drug release for the mucoadhesive buccal tablets in all formulations followed the first order model as the $R^2$ value is much higher compared to the zero order model. The high n-value which is more than 0.5 displayed by the Korsmeyer-Peppas model also confirmed that the rate of drug release followed a non-Fickian diffusion pattern. The results are shown in table 8 and fig 8-11.

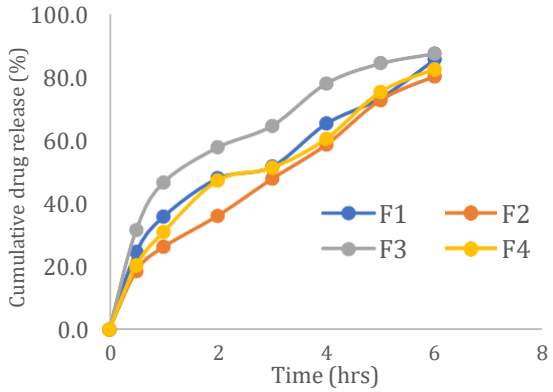


**Figure 8: The zero order model for the rate of drug release**

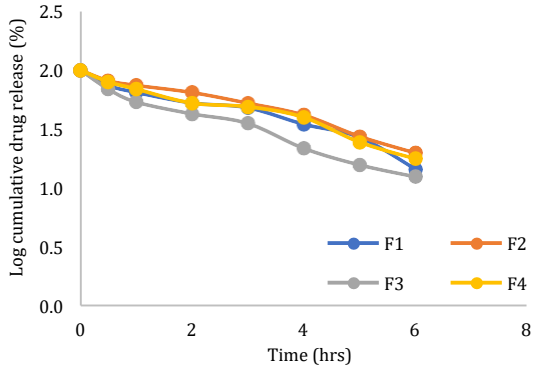


**Figure 9: The first order model the rate of drug release**

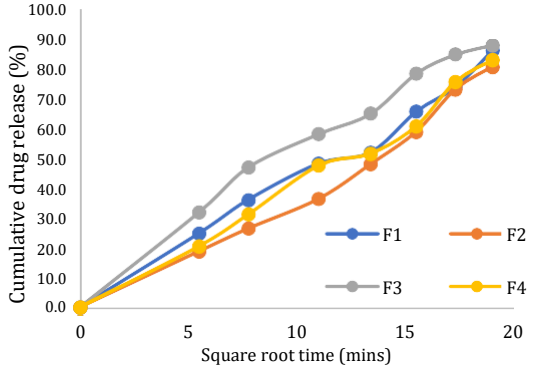


**Figure 10: The Higuchi's model for the rate of drug release**

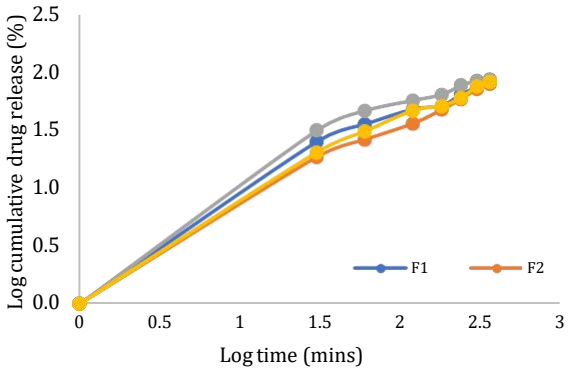


**Figure 11: The Korsmeyer-Peppas model for the rate of drug release**

### *Ex vivo* mucoadhesion time

All the tablets have a mucoadhesion time of more than 6 hours which was within the range of 4-8 hours for a standard mucoadhesive buccal drug delivery. The longest time of residence was shown by F3 (6.45 hours) and the shortest residence time was shown by F2 (6.05 hours). This determined that tablets with acacia gum have stronger mucoadhesion strength compared to the ones formulated with chitosan. The results are shown in table 9 and fig 12.

**Table 9: The ex vivo mucoadhesion time of the tablets**

| Formulation | Time taken (hrs) |
|---|---|
| F1 | 6.25 |
| F2 | 6.05 |
| F3 | 6.45 |
| F4 | 6.3 |

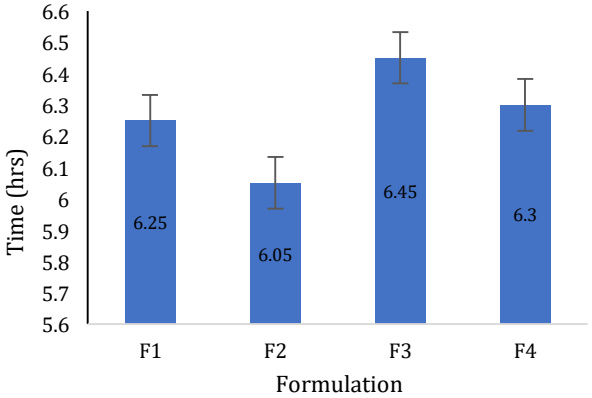


**Figure 12: The respective *ex vivo* mucoadhesion time for the different formulation**

### CONCLUSION

From this study, it was determined that the drug used and the natural polymers chosen were compatible with each other. The four formulations were observed to have some similarities in their general appearances, thickness, weight variation and degree to withstand friability. However, the

different formulations also produced tablets of varying hardness, with different degrees of *in vitro* swelling, *in vitro* dissolution and *ex-vivo* mucoadhesion time. It can be confirmed F3 had the highest potential among the other formulations and hold the highest degree of hardness, swelling, the longest residence time and the highest drug release profile. In the near future, it is hoped that this formulation can see its chance of being selected for further investigation and research regarding the ability to overcome first-pass metabolism effect by using the mucoadhesive buccal drug administration.

**ACKNOWLEDGEMENT**

This work was financed by MAHSA University, Malaysia. We are truly grateful to MAHSA for giving this opportunity.

**REFERENCES**

Abu-Huwaij, R., Assaf, S., Salem, M. and Sallam, A. 2007. Mucoadhesive dosage form of lidocaine hydrochloride. *Drug Development and Industrial Pharmacy* 33: 855-864.

Ahmed, S.F., Khan, I. and Saudagar, F. 2014. Formulation and comparative evaluation of mucoadhesive buccal tablet of losartan potassium. *Indo American Journal of Pharmceutical Research* 4(12): 5850-5857.

Alanazi, F.K., Abdel Rahman, A.A., Mahrous, G.M. and Alsarra, I.A. 2007. Formulation and physicochemical characterization of buccoadhesive films containing ketorolac. *Journal of Drug Delivery Science and Technology* 17 (1): 183-192.

Balaji, A., Radhika, V. and Goud, V. 2014. Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. *International Journal of Pharmceutical Sciences and Research* 5(11): 4699-4708.

Cafaggi, S., Leardi, R., Parodi, B., Caviglioli, G., Russo, E. and Bignardi, G. 2006. Preparation and evaluation of a chitosan salt-polymer 407 based matrix for buccal drug delivery. *Journal of Controlled Release* 102: 159-169.

Giannola, I.G., Caro, V.D., Giandalia, G., Siragusa, M.G., Tripodo, C., Floren, A.M. and Campisi, G. 2007. Release of naltrexone on buccal mucosa: permeation studies, histological aspects and matrix system design. *European Journal of Pharmaceutics and Biopharmaceutics* 67: 425-433.

Gosmawi, S. and Naik, S. 2014. Natural gums and its pharmaceutical applications. *Journal of Scientific and Innovative Research* 3(1): 112-121.

Juliano, C., Cossu, M., Pigozzi, P., Rassu, G. and Giunchedi, P. 2008. Preparation, *in vitro* characterization and preliminary *in vivo* evaluation of buccal polymeric films containing clorhexidine. *American Association of Pharmaceutical Scientists* 9(4): 1153-1158.

Kaundal, A., Kumar, P. and Chaudhary, A. 2015. A review on mucoadhesive buccal tablets prepared using natural and synthetic polymers.*World Journal of Pharmacy and Pharmaceutical Sciences* 4(7): 475-500.

Khanna, R., Agarwal, A.P. and Ahuja, A. 1996. Preparation and evaluation of bioerodible buccal tablets containing clotrimazole. *International Journal of Pharmaceutics* 138: 67-73.

Munasur, A.P., Pillay, V., Chetty, D.J. and Govender, T. 2006. Statistical optimization of mucoadhesivity and characterisation of multipolymeric propanolol matrices for buccal therapy. *International Journal of Pharmaceutics* 323: 43-51.