rescifar REVISTA ESPAÑOLA DE CIENCIAS FARMACÉUTICAS

Biocompatibility of the synthetic biomimetic membrane PermeaPad® with the mucosa of the oral

El Moussaoui El Masnaoui Salima *[1], Mallandrich Miret Mireia[1,4], Garrós Aristizabal Núria[1], Calpena Campmany Ana Cristina[1,4], Rodríguez Laguna María José[2], Fernández Campos Francisco[3]

[1] Departament de Farmàcia, Tecnologia Farmacèutica i Fisicoquímica, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII 27-31, 08028 Barcelona, Spain.
[2] Departament de Bioquímica i Fisiologia, Faculty of Pharmacy and Food Sciences, University of Barcelona, Av. Joan XXIII 27-31, 08028 Barcelona, Spain.
[3] Reig-Jofre Laboratories, Av. de les Flors s/n, 08970 Sant Joan Despí, Spain.
[4] Institut de Nanociència i Nanotecnologia IN2UB, Universitat de Barcelona, 08028 Barcelona, Spain
*Correspondencia: selmouel9@alumnes.ub.edu

1. Introduction

Animal studies are expensive and complex procedures that require a lot of bureaucracy and material and human resources. To all this, we must add the most important, the ethical and moral aspect of testing drugs and other products on animals.

The development of synthetic biomimetic membranes aims to provide a simple solution to all these problems. PermeaPad® biomimetic membranes have been developed to simulate passive mass transfer across different barriers in the body (GIT, buccal, nasal) [1].

To analyze the biocompatibility of these membranes, the permeation results of sodium alginate and hyaluronic acid hydrogel containing 2 % ketorolac tromethamine (KT) through the oral mucosa and the PermeaPad® membranes were correlated.

2. Material and Methods

2.1. Materials

Reagents: Sodium alginate, Ketorolac tromethamine, Nipagin, Nipasol, Hyaluronic acids, Na2HPO4 and KH2PO4, KCl, CaCl, Hepes, and glucose. The purified water. All the other chemicals and reagents used in the study were of analytical grade.

Tissue: Buccal and sublingual (SL) mucosae (Landrace Large White race) were provided by the Bellvitge animal facility services. The Ethics Committee of Animal Experimentation of the University of Barcelona approved the Study Protocol (approved on 10/01/2019). A thickness of 500 μm was dermatomized to carry out the test.

2.2. Methods

For the permeation test, 0.64 cm2 Franz-type diffusion cells were used. The receiving medium consisted of Hank's solution. 400 mg ± 10 mg of KT hydrogel were seeded, 300 μl of sample were extracted at times 0.5, 1, 2, 3, 4, 5, and 6 h, replacing the same volume of Hank's solution after each intake. The formulation was tested on buccal and SL mucosa and on PermeaPad® biomimetic membranes under an infinite dose regimen. KT content was analyzed by HPLC. The permeation parameters were calculated. After 6 h rehearsal, the KT retained in the mucosa was extracted [2].

The ex vivo permeation results and parameters were compared. For this, a one-way ANOVA statistical study was carried out. Furthermore,

Table 1. Biopharmaceutical KT permeation parameters under an infinite dose regimen according to first-order kinetics. Results are expressed as Mean ± SD (n = 3).

Parameter	Buccal Mucosa	Sublingual Mucosa	PermeaPad®	p-values
AP (mg/cm²)	3.79± 0.24	3.86 ± 0.25	3.04 ± 0.67	0.943
AR (mg/cm²)	0.12 ± 0.37	0.15 ± 0.16	0.35 ± 0.14	0.003**
Css (µg/mL)	1.13 ± 0.04	1.21 ± 0.05	1.36 ± 0.14	0.167
Jss (mg/h·cm²)	0.66 ± 0.02	0.71 ± 0.03	0.79 ± 0.08	0.181
Kp(cm/h)	0.052 ± 0.002	0.056 ± 0.002	0.062 ± 0.007	0.216

the correlation between the amounts of KT permeated through PermeaPad® vs. through buccal and SL mucosa at each time was calculated with the help of GraphPad software.

3. Results and Discussion

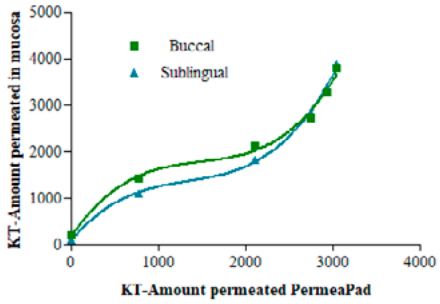

Fig. 1 Correlation of the KT amounts (µg/cm2) permeated through the PermeaPad® membrane and buccal mucosa (green) and PermeaPad® and SL mucosa (blue).

The Pearson regression coefficient (rp2) was 0.94 between PermeaPad® and buccal mucosa and 0.95 between PermeaPad® membrane and SL mucosa, showing a strong positive correlation (Fig 1). The correlations of the permeations through the mucosa of the oral cavity with the biomimetic membrane were adjusted to different mathematical models, giving an excellent fit (r2 of 0.993 in buccal mucosa vs. PermeaPad® and r2 of 0.998 in SL mucosa vs. PermeaPad®) for the third-order polynomial equation. This adjustment would allow us to predict from the results obtained through the PermeaPad® membrane the results that the buccal and SL mucosa would give, according to the following equations:

$$\text{Buccal } A_{KT} = 165.9x^3+2.8x^2-0.0017x+3.910^{-7}$$

$$\text{SL } A_{KT} = 86.4x^3+2.2x^2-0.0014-3.7\ 10^{-7}$$

where AKT is the amount of KT permeated through the mucosae for each time and x the amount of KT permeated through the PermeaPad® at each time.

In addition, a statistical study (one-way ANOVA) was performed between permeation parameters. The results were not statistically significant for all parameters except for the retained amounts of KT (Table 1). The results were that the two mucosae were able to retain more than twice as much KT as the PermeaPad® membrane.

4. Conclusion

Considering all these results, it can be concluded that, the PermeaPad® membran is able to predict with a high correlation the permeation kinetics of KT both in buccal and SL mucosa. The permeations correlation between the biomimetic membrane and the mucosae allows an excellent fit to the third-order polynomial model, thus providing a mathematical model to predict the KT amounts that could permeate living tissues using synthetic biomimetic membranes. The comparison of biopharmaceutical parameters did not show significant differences between the membrane ($p < 0.05$), although a lower drug retention capacity was observed in the PermeaPad® membrane compared to the buccal and SL mucosa ($p = 0.003$).

Acknowledgment

Our sincere thanks to the innoME GmbH company for donating the PermeaPad® biomimetic membranes.

References

1. HA Bibi, R Holm, A Bauer-Brandl. Use of Permeapad® for prediction of buccal absorption: A comparison to in vitro, ex vivo and in vivo method. Eur J Pharm Sci. 2016;93:399–404. doi: 10.1016/j.ejps.2016.08.041.

2. S El Moussaoui et al. Topical Mucoadhesive Alginate-Based Hydrogel Loading Ketorolac for Pain Management after Pharmacotherapy, Ablation or Surgical Removal in Condyloma Acuminata. MDPI Gels, pp. 1–20, 2021.

Este trabajo debe ser citado como:

El Moussaoui El Masnaoui S, Mallandrich Miret M, Garrós Aristizabal N, Calpena Campmany AC, Rodríguez Laguna MJ, Fernández CF. Biocompatibility of the synthetic biomimetic membrane PermeaPad® with the mucosa of the oral. Rev Esp Cien Farm. 2021;2(2):148-50.