TRANSLATIONAL POTENTIAL OF MICROARRAY PATCHES CONTAINING AMOXICILLIN SODIUM: A PRIMARY PACKAGING STUDY

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INTRODUCTION

An amoxicillin (AMX) sodium-containing microarray patch (MAP) has been fabricated. This consists of a hydrogel-forming microneedle (MN) array and an AMX sodium-containing reservoir. The improper primary packaging, storage and handling of medicines in humid and hot countries may result in unintentional degradation of active pharmaceutical ingredients. As a result, the use of such substandard medicines is a major public health concern in countries with those environmental conditions (1). AMX sodium is inherently unstable, as hydrolysis occurs, due to the presence of a labile ß-lactam ring. The research presented here seeks to investigate the effects of primary packaging on MN array integrity and AMX sodium stability in AMX sodium-containing MAPs.

METHODS

1. Preparation of hydrogel-forming MN arrays, AMX sodium-containing reservoirs and AMX sodium-containing MAPs

Novel hydrogel-forming MN arrays were prepared from hydrogel formulation, 15% w/w poly(vinyl alcohol) (PVA), 10% w/w poly(vinyl pyrrolidone) (PVP) and 1.5% w/w citric acid (**Figure 1(A) and 1(B)**). Using the compression method, AMX sodium-containing reservoirs were prepared using 95% w/w AMX sodium and 5% w/w sodium starch glycolate (SSG). Hydrogel-forming MN arrays and AMX sodium-containing reservoirs were combined to form AMX sodium-containing MAPs using release liner, Parafilm M® and Tegaderm™ film.

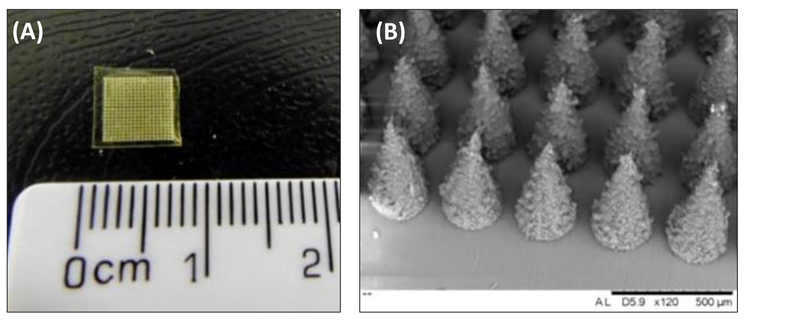

Figure 1. Hydrogel-forming MN arrays composed of 361 needles, each of height, 600 µm; **(A)** Digital Image and **(B)** Scanning Electron Micrograph (SEM).

2. Packaging

Hydrogel-forming MN arrays, AMX sodium-containing reservoirs and AMX sodium-containing MAPs were packaged in moisture-impermeable packaging and stored at 40°C and 75% RH for 168 days. Two different primary packaging was tested, namely, Protect 470 MIL-131 K® (Protect™ 470) foil (**Figure 2**) and heat-sealable poly(ester) foil. Hydrogel-forming MN arrays, AMX sodium-containing reservoirs and AMX sodium-containing MAPs not in packaging were also investigated.

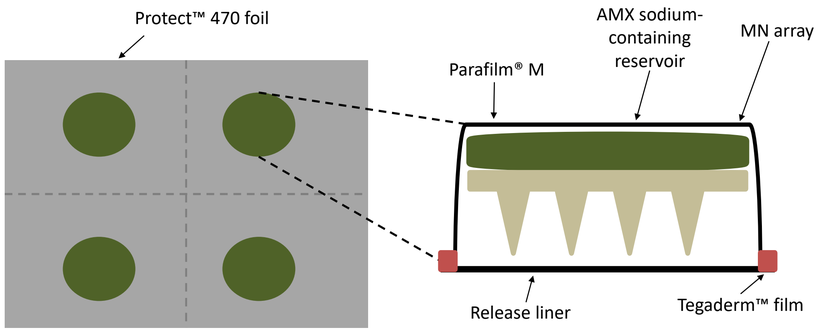

Figure 2. Schematic representation of AMX sodium-containing MAPs packaged in Protect™ 470 foil.

3. Characterisation following accelerated storage

At pre-defined intervals (7, 28, 84 and 168 days), samples were removed from accelerated storage. The insertion capabilities of hydrogel-forming MN arrays were investigated using a previously-reported method, using Parafilm® M (2). Physical characterisation of the reservoir was carried out. Tablet mass, diameter, thickness, break force and hardness was measured.

AMX sodium-containing reservoirs were also individually placed in ammonium acetate buffer (pH 5.76) and the recovery was determined *via* high performance liquid chromatography (HPLC). For the AMX sodium-containing MAPs, the recovery of AMX sodium from both the hydrogel-forming MN array and AMX sodium-containing reservoir was assessed separately using HPLC.

RESULTS AND DISCUSSION

Hydrogel-forming MN arrays were mechanically strong and consistently robust after storage for 168 days in Protect™ 470 foil (**Figure 2(A)**). This was exemplified by insertion of hydrogel-forming MN arrays into the skin simulant, with 21.33 ± 6.88% holes still created in layer 3, consistent with results from previously published studies (3). The insertion capabilities were not obtained when hydrogel-forming MN arrays were packaged in poly(ester) foil at day 28 and thereafter (**Figure 2(B)**). With regards to hydrogel-forming MN arrays not packaged, these results show mechanically strong and robust hydrogel-forming MN arrays only until day 28 (**Figure 2(C)**).

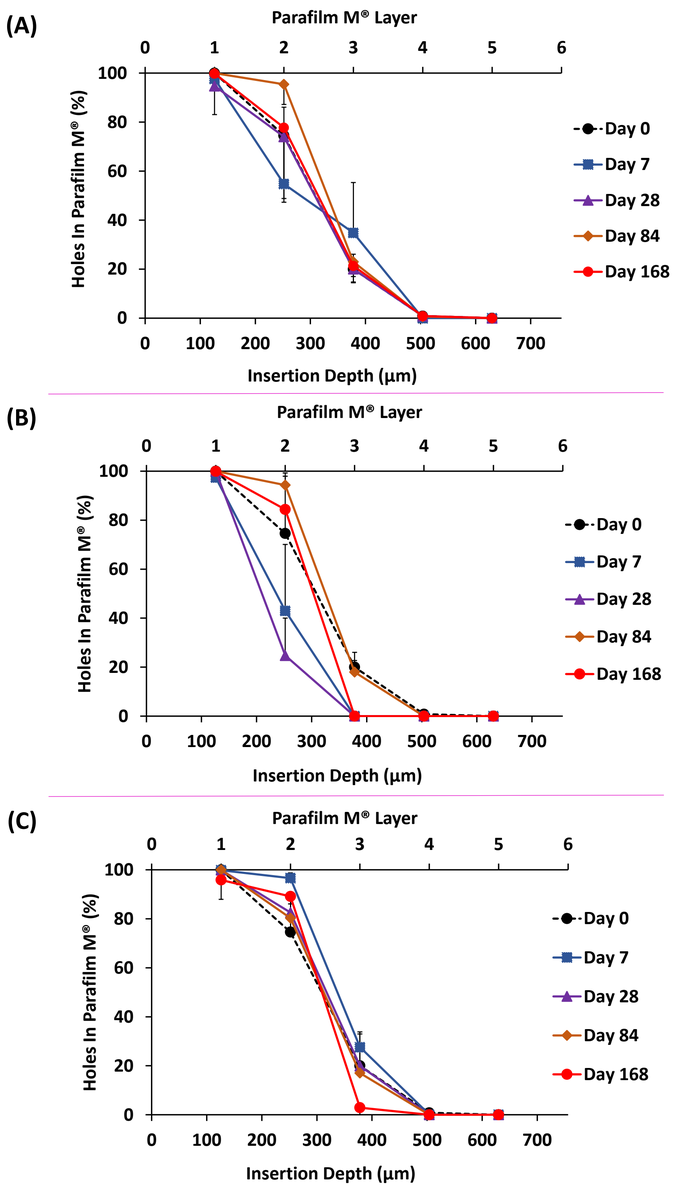

Figure 2. Insertion studies of hydrogel-forming MN arrays into skin simulant packaged in **(A)** Protect™ 470 foil; **(B)** Poly(ester) foil and **(C)** Not packaged (Means ± SD., n≥3).

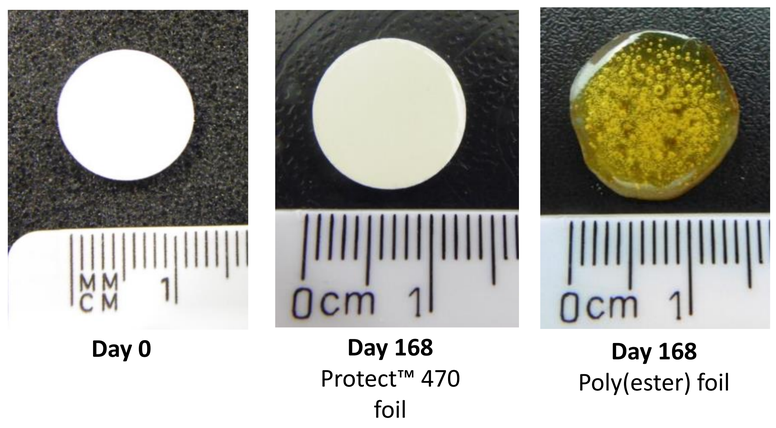

Figure 3. AMX sodium-containing reservoirs following accelerated storage.

Physical characterisation of AMX sodium-containing reservoirs in both packaging at specified time points is displayed in **Tables 1(A) and 1(B)**. AMX sodium-containing reservoirs not packaged could not be analysed because they could not be easily handled.

Table 1. Physical characterisation of AMX sodium-containing reservoirs packaged in; **(A)** Protect™ 470 foil and **(B)** Poly(ester) foil (Means ± SD., n≥3).

(A)	Protect™ 470 foil				
	Time (day)				
Parameter	**0**	**7**	**28**	**84**	**168**
Mass (mg)	194.68 ± 0.00	193.75 ± 0.00	200.45 ± 0.00	201.28 ± 0.00	200.53 ± 0.00
Diameter (mm)	13.02 ± 0.01	13.04 ± 0.01	13.03 ± 0.05	13.04 ± 0.02	13.03 ± 0.01
Thickness (mm)	1.30 ± 0.03	1.32 ± 0.03	1.29 ± 0.04	1.32 ± 0.03	1.33 ± 0.02
Break force (N)	2.77 ± 0.55	2.97 ± 0.48	2.79 ± 0.45	2.71 ± 0.33	2.65 ± 0.42
Hardness (N)	24.00 ± 6.00	31.67 ± 3.06	28.75 ± 4.11	27.00 ± 4.08	26.50 ± 4.20

(B)	Poly(ester) foil				
	Time (day)				
Parameter	**0**	**7**	**28**	**84**	**168**
Mass (mg)	194.68 ± 0.00	193.13 ± 0.00	212.78 ± 0.01	233.68 ± 0.00	249.53 ± 0.00
Diameter (mm)	13.02 ± 0.01	13.15 ± 0.02	13.24 ± 0.09	13.32 ± 0.05	15.25 ± 2.78
Thickness (mm)	1.30 ± 0.03	1.37 ± 0.02	1.38 ± 0.00	1.39 ± 0.01	1.75 ± 0.37
Break force (N)	2.77 ± 0.55	2.60 ± 0.35	2.60 ± 0.18	3.43 ± 0.58	9.90 ± 2.07
Hardness (N)	24.00 ± 6.00	25.75 ± 6.24	34.25 ± 5.12	51.00 ± 2.65	40.50 ± 1.91

AMX sodium-containing reservoirs demonstrate uniform mass, physical dimensions, break force and hardness when packaged in Protect™ 470 foil. However, AMX sodium-containing reservoirs packaged in poly(ester) foil increased in mass, diameter and thickness after 168 days. With this, they required a higher force to break (p= 0.0286) and were significantly harder to crush (p= 0.0294).

The recovery of AMX sodium from AMX sodium-containing reservoirs is illustrated in **Figure 4.** After 168 days, the % of AMX sodium recovered from AMX sodium-containing reservoirs packaged in Protect™ 470 foil was 107.54 ± 6.16% whereas in poly(ester) foil was 0.03 ± 0.02%. This significant difference (p=<0.0001) is most likely due to the degradation of AMX sodium in the reservoir due to aqueous hydrolysis by the imbibed moisture.

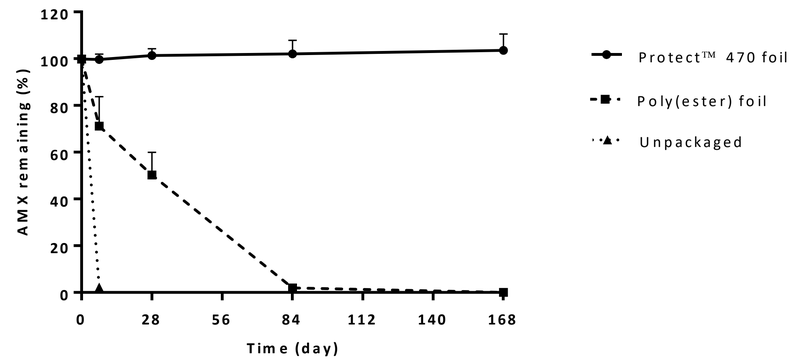

Figure 4. Recovery of AMX sodium from AMX sodium-containing reservoirs (Means ± SD., n≥3).

Additional stability testing of packaged AMX sodium-containing MAPs in Protect™ 470 foil demonstrated that AMX sodium did not migrate into the adjacent hydrogel-forming MN arrays.

CONCLUSION

Primary packaging is imperative in maintaining the efficacy and stability of labile medicines. Of the two different primary packaging investigated, this study successfully demonstrates that Protect™ 470 foil is more effective than poly(ester) foil in terms of moisture barrier function and temperature resistance. This work indicates the importance of investigating the stability of other drugs, in appropriate primary packaging, intended for MN-mediated transdermal delivery so that they are are 'fit for purpose' when they reach the end-user. Future work will include qualitative studies to assess MN patch usability.

REFERENCES

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