In Vitro Drug Release and In Vivo Efficacious Study of Lyogels Containing Hydrocortisone for the Treatment of Eczema

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ABSTRACT SUMMARY
Lyogels are three dimensional gel networks in which the pores are filled with aqueous and non-aqueous solvents. Previously, a stable hydroxylpropyl methylcellulose lyogel was successfully formulated and characterised. Here, the in vitro drug release performance of lyogels containing hydrocortisone was evaluated using Franz diffusion cells. The in vivo efficacy on eczema was assessed using Balb/c mice. The mice were first subjected to induction of eczema. After 7 days of lyogel treatment, the serum immunoglobulin E levels and infiltration of inflammatory mediators were assessed. All data was analyzed using ANOVA (one-way) and p-values less than 0.05 were considered statistically significant. From the results, the lyogels showed significantly higher drug release profile compared to hydrocortisone commercial cream. The histopathology evaluation revealed that hydrocortisone lyogels demonstrated a higher inflammatory suppressive effect compared to the commercial cream. These findings infer that lyogel delivers hydrophobic drugs such as hydrocortisone more effectively compared to the topical cream.

INTRODUCTION
Hydrogels are widely accepted by the patients for topical application because it is easy to apply and rinse off compared to creams, while giving a cooling relief of painful burning and itching to eczematic skin. However, the hydrophilic nature of hydrogel matrices makes them difficult to solubilise hydrophobic drugs such as corticosteroids and thus restrict their applications as efficient topical drug delivery systems for hydrophobic drugs. Lyogels are gel systems with a three dimensional network in which the pores filled with miscible aqueous and non-aqueous solvents (‘lyo’ means ‘solvents’ in Greek). Preformulation studies showed that the lyogels are stable when polymers are dispersed in 80-90% non-aqueous solvent and 10-20% of water. Lyogels may be useful for topical delivery of hydrophobic drugs because it is likely to solubilise higher amount of hydrophobic drugs than hydrogel. Among other advantages of the lyogels is the presence of non-aqueous solvents which are typically permeation enhancers (e.g. propylene glycol, oleic acid) which can maximise the partitioning of the active gradient into the skin tissue. The higher percentage of non-aqueous solvent used also makes lyogels less susceptible to microbial growth.

Anuwi & Ng has successfully developed a stable hydroxylpropyl methylcellulose (HPMC) lyogel. In this study, the drug release of the HPMC lyogel containing 1% hydrocortisone was performed using Franz diffusion cells. Then, the in vivo efficacy was assessed using eczematous induced Balb/c mice.

EXPERIMENTAL METHODS
The composition of lyogel containing 1% hydrocortisone is listed in Table 1.

Table 1: Formulation of 1% hydrocortisone lyogel
<table>
<thead>
<tr>
<th>Constituents</th>
<th>Weight (g)</th>
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<tbody>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
</tr>
<tr>
<td>HPMC</td>
<td>2</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>75</td>
</tr>
<tr>
<td>Water</td>
<td>25</td>
</tr>
</tbody>
</table>

The hydrocortisone drug release study from lyogel and cream was also performed using Franz diffusion cells. In the in vivo study, Balb/c mice were subjected to induction with 0.5% DNFB solution to produce the eczematic skin condition. After one week treatment, the serum IgE levels were measured using ELISA and infiltration of inflammatory mediators in the skin was assessed via histopathology H&E staining. The eczematous mice were segregated into four groups: Group 1 was treated with hydrocortisone lyogels while Group 2 was treated with drug-free lyogels. Group 3 was applied with commercial 1% hydrocortisone cream while Group 4 was applied with saline solution. All animal study was approved by Animal Ethics Committee Universiti Kebangsaan Malaysia (UKMAEC) with the approval number FF/2013/FF/15-MAY/520-AUG.-2013-JAN.-2014. All data was analyzed using ANOVA (one-way) and p-values less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSION
Figure 1 shows the cumulative amount of hydrocortisone permeated through cellulose acetate membrane and mice skin for lyogels and creams. It shows that the lyogel formulation has a greater permeation profile of hydrocortisone for both membranes as compared to the commercial cream (p<0.05).
A significant difference of hydrocortisone released across cellulose acetate membrane from cream (p<0.05)

A significant difference of hydrocortisone released across mice skin from cream (p<0.05)

Figure 1. Hydrocortisone drug release profile of lyogel and cream (n=3).

The serum IgE levels are shown in Figure 2. The serum IgE level of Group I mice was lower as compared to Group II and III but showed no significant difference with Group IV after one week. This result suggests that the hydrocortisone lyogel was more effective in resolving inflammatory reaction associated with eczema when compared to commercial cream.

Figure 2. Serum IgE concentration

A significant different compared to group I (p<0.05)

Figure 3. Histology H&E staining of full thickness mice skin Group 1 to 4 after 7-day treatment (Mag 5x). NE - non- eczematous epidermis, E- eczematous epidermis, IN - neutrophils infiltration.

CONCLUSION

Lyogel hold promise as a potential vehicle for corticosteroids for skin inflammation. It not only possesses a desirable topical gel characteristics, the hydrocortisone lyogel also resolves inflammatory manifestation more effectively than the commercial hydrocortisone cream, as observed by the higher drug release, reduced serum IgE level, decreased infiltration of neutrophils and improved erythema.

REFERENCES


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