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Design optimisation and characterisation of films for delivering poorly soluble hydrophobic drugs to wounds

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SUMMARY

Despite advancements in wound management, chronic wounds still fail to heal in an appropriate time and manner. Hydrophobic drugs of interest to the pharmaceutical industry exist that are suggested to reduce inflammation and aid in the wound healing process; however, delivering these drugs poses a challenge both in terms of ease of formulation processing and drug release characteristics when applied *in vivo*. Naturally occurring, biocompatible, and bioactive excipients, such as hydroxyethyl cellulose (HEC) and citric acid (CA) are hydrophilic and widely used in wound management and delivery of soluble drugs. However, hydrophobic drugs are not compatible in this environment without the addition of molecules, such as β-cyclodextrin (βCD), which acts as a drug carrier and allows drug delivery. This study investigated the use of CA in formulation development to achieve crosslinking of HEC and βCD to allow the incorporation of poorly soluble model drugs. The prepared films have been characterized for their functional physico-chemical properties relevant for wound healing applications.

INTRODUCTION

Effective treatment of chronic wounds in a timely and cost effective rate is a clinical concern. Current modern wound dressings such as films provide a moist wound environment, enabling proper cellular and molecular function (e.g. cell migration) to ensure normal wound healing progression. Despite advancements, chronic wounds are still difficult to treat in a timely manner. There is therefore the need for more advanced dressings such as medicated dressings loaded with drugs that can take an active part in the wound healing process. Various hydrophobic drugs of interest exist that are suggested to reduce inflammation and aid in wound healing. However, delivering these drugs poses a challenge, especially for films which are thin with have minimal physical volume for effective drug incorporation to achieve uniform distribution and dispersion. Furthermore, the naturally occurring, polymers and excipients used for preparing film based dressings, such as hydroxyethyl cellulose (HEC) and citric acid (CA) are hydrophilic. Therefore, hydrophobic drugs are not compatible in without addition of molecules such as β-cyclodextrin (βCD), which acts as a solubilizers and allows drug delivery.

MATERIALS AND METHODS

Films were formulated by first preparing HEC gels at concentrations of 2, 3 and 4% w/v, under magnetic stirring. Then CA 0.2% w/w and βCD 0.1% w/w solutions were added as cross linker and drug solubilizer, respectively, left to stir (3 hrs) and then left to stand (1 hr) undisturbed. The gels were cast

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(20g & 30g) and dried at 50˚C (24 hrs) to form the initial films. These films were then cured at 145˚C (5 mins), washed with water and isopropyl alcohol (1 hr), and dried again at 30˚C (24 hrs) (Sampatrao et al., 2018). The cured films were characterised for mechanical strength, adhesion, and swelling capacity. Further, scanning electron microscopy (SEM), X-ray diffraction (XRD), thermo-gravimetric analysis (TGA) and nuclear magnetic resonance (NMR) spectroscopy were used to select the most optimised formulation for drug loading and eventual release studies.

RESULTS AND DISCUSSION

All film concentrations trialled were flexible and clear, which was supported by the mechanical data (data not shown). The swelling profile (Fig. 1) of the films suggested that a hydrogel matrix had formed between the crosslinked HEC-CA-βCD, which was confirmed by NMR.

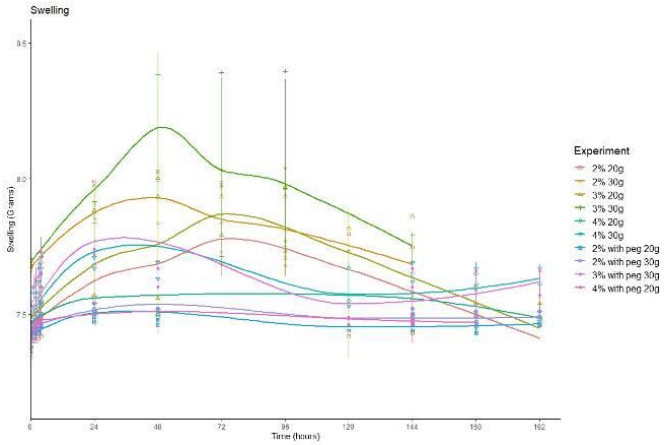

Fig. 1. *Swelling profile of all HEC films with and without PEG.*

The addition of polyethylene glycol (PEG) resulted in films with lower water handling ability (Fig. 1). Under SEM, the films appeared uniform and smooth, due to the absence of any pores. This helps to explain the reason for the low volume of exudate the samples could handle. Interestingly, the NMR data showed the crosslinking between HEC-CA-βCD (Fig. 2a, red arrow). This disappeared when a model insoluble drug was loaded (Fig. 2b), and suggests that the drug was successfully loaded and molecularly incorporated.

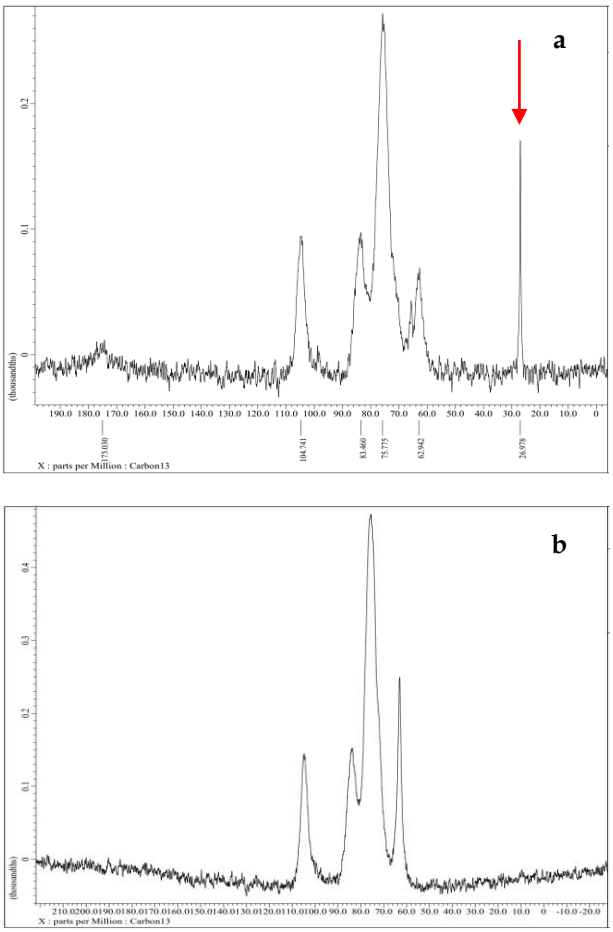

Fig. 2. *a) NMR spectra of a HEC film, red arrow hightlights the HEC-CA-βCD complex, b) shows a typical drug loaded film with the same spectra; however, the complex is now missing.*

CONCLUSIONS

3% HEC 30g film outperformed the others in the swelling tests (Fig. 1), while the adhesion and tensile strength tests were all comparable (data not shown). A shift in the molecular structure of the films was visible in the NMR spectra (Fig. 2b), suggesting that the drug was successfully incorporated in the film matrix. The films need to be tested further to determine the effect of curing/loading on their mechanical properties.

REFERENCES

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